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<p>(54) Title: INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES</p>		
<p>(57) Abstract</p> <p>Compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein R₁ is (a) hydrogen, (b) lower alkyl, (c) alkenyl, (d) alkoxy, (e) thioalkoxy, (f) halo, (g) haloalkyl, (h) aryl -L₂-, and (i) heterocyclic -L₂-; R₂ is selected from (a) formula (1), (b) -C(O)NH-CH(R₁₄)-C(O)OR₁₅, (c) formula (2), (d) -C(O)NH-CH(R₁₄)-C(O)NHSO₂R₁₆, (e) -C(O)NH-CH(R₁₄)-tetrazolyl, (f) -C(O)NH-heterocyclic, and (g) -C(O)NH-CH(R₁₄)-C(O)NR₁₇R₁₈; R₃ is substituted or unsubstituted heterocyclic or aryl, substituted or unsubstituted cycloalkyl or cycloalkenyl, formula (3), and -P(W)RR³R^{3'}; R₄ is hydrogen, lower alkyl, haloalkyl, halogen, aryl, arylalkyl, heterocyclic, or (heterocyclic)alkyl; L₁ is absent or is selected from (a) -L₄-N(R₅)-L₅-, (b) -L₄-O-L₅-, (c) -L₄-S(O)_n-L₅-, (d) -L₄-L₆-C(W)-N(R₅)-L₅-, (e) -L₄-L₆-S(O)_m-N(R₅)-L₅-, (f) -L₄-N(R₅)-C(W)-L₇-L₅-, (g) -L₄-N(R₅)-S(O)_p-L₇-L₅-, (h) optionally substituted alkylene, (i) optionally substituted alkenylene, (j) optionally substituted alkynylene, (k) a covalent bond, (l) formula (4), and (m) formula (5) are inhibitors of protein isoprenyl transferases. Also disclosed are protein isoprenyl transferase inhibiting compositions and a method of inhibiting protein isoprenyl transferases.</p> <div style="text-align: right;"> </div>		

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INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES

5

Technical Field

10 The present invention relates to novel compounds which are useful in inhibiting protein isoprenyl transferases (for example, protein farnesyltransferase and protein geranylgeranyltransferase) and the farnesylation or geranylgeranylation of the oncogene protein Ras and other related small g-proteins, compositions containing such compounds and methods of using such compounds.

15

Background of the Invention

 Ras oncogenes are the most frequently identified activated oncogenes in human tumors. Transformed protein Ras is involved in the proliferation of cancer cells. The Ras must be farnesylated before this proliferation can occur. Farnesylation of Ras by farnesyl
20 pyrophosphate (FPP) is effected by protein farnesyltransferase. Inhibition of protein farnesyltransferase, and thereby farnesylation of the Ras protein, blocks the ability of transformed cells to proliferate. Inhibition of protein geranylgeranyltransferase and, thereby, of geranylgeranylation of Ras proteins, also results in down regulation of Ras protein function.

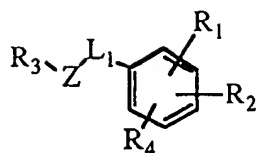
25 Activation of Ras and other related small g-proteins that are farnesylated and/or geranylated also partially mediates smooth muscle cell proliferation (Circulation, I-3: 88 (1993), which is hereby incorporated herein by reference). Inhibition of protein isoprenyl transferases, and thereby farnesylation or geranylgeranylation of the Ras protein, also aids in the prevention of intimal hyperplasia associated with restenosis and atherosclerosis, a
30 condition which compromises the success of angioplasty and surgical bypass for obstructive vascular lesions.

 There is therefore a need for compounds which are inhibitors of protein farnesyltransferase and protein geranylgeranyltransferase.

35

Summary of the Invention

 In its principle embodiment, the invention provides a compound having the formula:



I

or a pharmaceutically acceptable salt thereof, wherein

40 R_1 is selected from the group consisting of

- (1) hydrogen,
- (2) alkenyl,
- (3) alkynyl,
- (4) alkoxy,
- 45 (5) haloalkyl,
- (6) halogen,
- (7) loweralkyl,
- (8) thioalkoxy,
- (9) aryl- L_2 - wherein aryl is selected from the group consisting of

- 50 (a) phenyl,
- (b) naphthyl,
- (c) dihydronaphthyl,
- (d) tetrahydronaphthyl,
- (e) indanyl, and
- 55 (f) indenyl

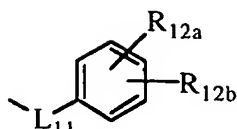
wherein (a)-(f) are unsubstituted or substituted with at least one of X, Y,

or Z wherein X, Y, and Z are independently selected from the group consisting of

- alkenyl,
- 60 alkynyl,
- alkoxy,
- aryl,
- carboxy,
- cyano,
- 65 halogen,
- haloalkyl,
- hydroxy,
- hydroxyalkyl,
- loweralkyl,
- 70 nitro,

- N-protected amino, and
 -NRR' wherein R and R' are independently selected
 from the group consisting of
 hydrogen and
 loweralkyl,
 oxo (=O), and
 thioalkoxy and
 L₂ is absent or is selected from the group consisting of
 -CH₂-,
 -CH₂CH₂-,
 -CH(CH₃)-,
 -O-,
 -C(O)-,
 -S(O)_q wherein q is 0, 1 or 2, and
 -N(R)-, and
 (10) heterocycle-L₂- wherein L₂ is as defined above and the heterocycle is
 unsubstituted or substituted with 1, 2, 3 or 4 substituents
 independently selected from the group consisting of
 (a) loweralkyl,
 (b) hydroxy,
 (c) hydroxyalkyl,
 (d) halogen
 (e) cyano,
 (f) nitro,
 (g) oxo (=O),
 (h) -NRR',
 (i) N-protected amino,
 (j) alkoxy,
 (k) thioalkoxy,
 (l) haloalkyl,
 (m) carboxy, and
 (n) aryl;

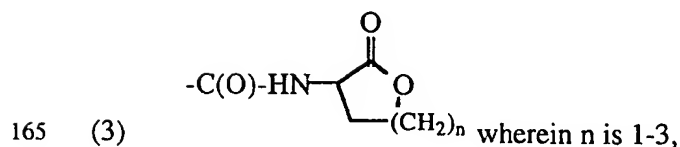
R₂ is selected from the group consisting of



- 105 (1) wherein L_{11} is selected from the group
 consisting of
 (a) a covalent bond,
 (b) $-C(W)N(R)-$ wherein R is defined previously and W is
 selected from the group consisting of O and S,
 110 (c) $-C(O)-$,
 (d) $-N(R)C(W)-$,
 (e) $-CH_2O-$,
 (f) $-C(O)O-$, and
 (g) $-CH_2N(R)-$,
 115 R_{12a} is selected from the group consisting of
 (a) hydrogen,
 (b) loweralkyl, and
 (c) $-C(O)OR_{13}$ wherein R_{13} is selected from the group
 consisting of
 120 hydrogen and
 a carboxy-protecting group, and
 R_{12b} is selected from the group consisting of
 (a) hydrogen and
 (b) loweralkyl,
 125 with the proviso that R_{12a} and R_{12b} are not both hydrogen,

- (2) $-L_{11}-C(R_{14})(R_v)-C(O)OR_{15}$ wherein L_{11} is defined previously,
 R_v is selected from the group consisting of
 (a) hydrogen and
 130 (b) loweralkyl,
 R_{15} is selected from the group consisting of
 (a) hydrogen,
 (b) alkanoyloxyalkyl,
 (c) loweralkyl, and
 135 (b) a carboxy-protecting group, and
 R_{14} is selected from the group consisting of
 (a) alkoxyalkyl,
 (b) alkoxyarylalkyl,

- 140 (c) alkoxycarbonylalkyl,
 (d) alkylsulfinylalkyl,
 (e) alkylsulfonylalkyl,
 (f) alkynyl,
 (g) aminoalkyl,
 (h) aminocarbonylalkyl,
 145 (i) aminothiocarbonylalkyl,
 (j) aryl,
 (k) arylalkyl,
 (l) carboxyalkyl,
 (m) cyanoalkyl,
 150 (n) cycloalkyl,
 (o) cycloalkylalkoxyalkyl,
 (p) cycloalkylalkyl,
 (q) (heterocyclic)alkyl,
 (r) hydroxyalkyl,
 155 (s) hydroxyarylalkyl,
 (t) loweralkyl,
 (u) sulfhydrylalkyl,
 (v) thioalkoxyalkyl wherein the thioalkoxyalkyl is
 unsubstituted or substituted with 1, 2, 3, or 4
 160 substituents selected from the group consisting of
 halogen,
 (w) thioalkoxyalkylamino, and
 (x) thiocycloalkyloxyalkyl,



- (4) $-\text{C}(\text{O})\text{NH}-\text{CH}(\text{R}_{14})-\text{C}(\text{O})\text{NHSO}_2\text{R}_{16}$ wherein R_{14} is defined previously
 and R_{16} is selected from the group consisting of
 170 (a) loweralkyl,
 (b) haloalkyl,
 (c) aryl wherein the aryl is unsubstituted or substituted with
 1, 2, 3, 4, or 5 substituents independently

- selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR'
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl, and
- (d) heterocycle wherein the heterocycle is unsubstituted or
substituted with substituents independently
selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR',
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl;
- (5) -C(O)NH-CH(R₁₄)-tetrazolyl wherein the tetrazole ring is unsubstituted
or substituted with loweralkyl or haloalkyl,
- (6) -L₁₁-heterocycle,

210

- (7) $-C(O)NH-CH(R_{14})-C(O)NR_{17}R_{18}$ wherein R_{14} is defined previously and R_{17} and R_{18} are independently selected from the group consisting of

215

- (a) hydrogen,
- (b) loweralkyl,
- (c) arylalkyl,
- (d) hydroxy, and
- (e) dialkylaminoalkyl,

220

- (8) $-C(O)OR_{15}$, and

- (9) $-C(O)NH-CH(R_{14})$ -heterocycle wherein R_{14} is as previously defined and the heterocycle is unsubstituted or substituted with loweralkyl or haloalkyl;

225

L_1 is absent or is selected from the group consisting of

- (1) $-L_4-N(R_5)-L_5-$ wherein L_4 is absent or selected from the group consisting of

230

- (a) C_1 -to- C_{10} -alkylene and
- (b) C_2 -to- C_{16} -alkenylene,

wherein the alkylene and alkenylene groups are unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

235

alkenyl,
alkenyloxy,
alkenyloxyalkyl,
alkenyl[S(O)_q]alkyl,
alkoxy,

240

alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2 hydroxyl substituents, with the proviso that no two hydroxyls are attached to the same carbon,

245

alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from the group consisting of

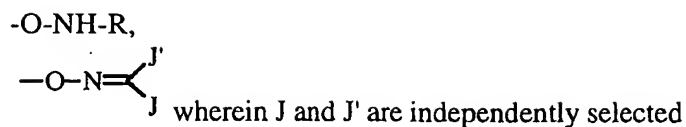
halogen and
cycloalkyl,
alkylsilyloxy,
250 alkyl[S(O)_q],
alkyl[S(O)_q]alkyl,
aryl wherein the aryl is unsubstituted or substituted with
1, 2, 3, 4, or 5 substituents independently
selected from the group consisting of
255 alkoxy wherein the alkoxy is unsubstituted or
substituted with substituents selected
from the group consisting of cycloalkyl,
aryl,
arylalkyl,
260 aryloxy wherein the aryloxy is unsubstituted or
substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of,
halogen,
265 nitro, and
-NRR',
cycloalkyl,
halogen,
loweralkyl,
270 hydroxyl,
nitro,
-NRR', and
-SO₂NRR',
arylalkoxy wherein the arylalkoxy is unsubstituted or
275 substituted with substituents selected from the
group consisting of alkoxy,
arylalkyl,
arylalkyl[S(O)_q]alkyl,
aryl[S(O)_q],
280 aryl[S(O)_q]alkyl wherein the aryl[S(O)_q]alkyl is
unsubstituted or substituted with 1, 2, 3, 4, or 5
substituents independently selected from
alkoxy and

loweralkyl,
285 arylalkoxyalkyl wherein the arylalkoxyalkyl is
unsubstituted or substituted with substituents
selected from the group consisting of
alkoxy, and
halogen,
290 aryloxy,
aryloxyalkyl wherein the aryloxyalkyl is unsubstituted or
substituted with substituents selected from the
group consisting of halogen,
carboxyl,
295 $-C(O)NR_C R_D$ wherein R_C and R_D are independently
selected from the group consisting of
hydrogen,
loweralkyl, and
alkoxycarbonyl or
300 R_C and R_D together with the nitrogen to which
they are attached form a ring selected
from the group consisting of
morpholine,
piperidine,
305 pyrrolidine
thiomorpholine,
thiomorpholine sulfone, and
thiomorpholine sulfoxide,
wherein the ring formed by R_C and R_D
310 together is unsubstituted or
substituted with 1 or 2
substituents independently
selected from the group consisting
of alkoxy and alkoxyalkyl,
315 cycloalkenyl wherein the cycloalkenyl is unsubstituted or
substituted with 1 or 2 substituents selected from
the group consisting of alkenyl,
cycloalkoxy,
cycloalkoxycarbonyl,
320 cycloalkoxyalkyl,

cycloalkyl wherein the cycloalkyl is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting
of aryl,
325 loweralkyl, and
alkanoyl,
cycloalkylalkoxy,
cycloalkylalkoxycarbonyl,
cycloalkylalkoxyalkyl,
330 cycloalkylalkyl,
cycloalkyl[S(O)_q]alkyl,
cycloalkylalkyl[S(O)_q]alkyl,
fluorenyl,
heterocycle wherein the heterocycle is unsubstituted or
335 substituted with 1, 2, 3, or 4 substituents
independently selected from the group
consisting of
alkoxy wherein the alkoxy is unsubstituted or
substituted with 1 or 2 substituents
340 independently selected from the group
consisting of aryl and cycloalkyl,
alkoxyalkyl wherein the alkoxyalkyl is
unsubstituted or substituted with 1 or 2
substituents independently selected from
345 the group consisting of
aryl and
cycloalkyl,
alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1 or 2
350 substituents independently selected from
the group consisting of
aryl and
cycloalkyl,
aryl wherein the aryl is unsubstituted or
355 substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of

360 alkanoyl,
alkoxy,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
nitro,
365 -NRR', and
thioalkoxy,
arylalkyl,
aryloxy,
cycloalkoxyalkyl,
370 cycloalkyl,
cycloalkylalkyl,
halogen,
heterocycle,
hydroxyl,
375 loweralkyl wherein the loweralkyl is
unsubstituted or substituted with 1, 2, or
3 substituents independently selected
from the group consisting of
heterocycle,
380 hydroxyl,
with the proviso that no two hydroxyls
are attached to the same carbon,
and
-NRR³R^{3'} wherein R³ and R^{3'} are
385 independently selected from the
group consisting of
hydrogen
aryl,
loweralkyl,
390 aryl,
arylalkyl,
heterocycle,
(heterocyclic)alkyl,
cycloalkyl, and

395 cycloalkylalkyl, and
 sulfhydryl,
 (heterocyclic)alkoxy,
 (heterocyclic)alkyl,
 (heterocyclic)alkyl[S(O)_q]alkyl,
 400 (heterocyclic)oxy,
 (heterocyclic)alkoxyalkyl,
 (heterocyclic)oxyalkyl,
 heterocycle[S(O)_q]alkyl,
 hydroxyl,
 405 hydroxyalkyl,
 imino,
 N-protected amino,
 =N-O-aryl, and
 =N-OH,
 410 =N-O-heterocycle wherein the heterocycle is
 unsubstituted or substituted with 1, 2, 3, or 4
 substituents independently selected from the
 group consisting of
 loweralkyl,
 415 hydroxy,
 hydroxyalkyl,
 halogen,
 cyano,
 nitro,
 420 oxo (=O),
 -NRR'
 N-protected amino,
 alkoxy,
 thioalkoxy,
 425 haloalkyl,
 carboxy, and
 aryl,
 =N-O-loweralkyl,
 -NR^{R3}R^{R3'},
 430 -NHNR_CR_D,
 -OG wherein G is a hydroxyl protecting group,



from the group consisting of

loweralkyl and

arylalkyl,

oxo,

oxyamino(alkyl)carbonylalkyl,

oxyamino(arylalkyl)carbonylalkyl,

oxyaminocarbonylalkyl,

-SO₂-A wherein A is selected from the group

consisting of

loweralkyl,

aryl, and

heterocycle

wherein the loweralkyl, aryl, and heterocycle are

unsubstituted or substituted with 1, 2, 3,

4, or 5 substituents independently

selected from the group consisting of

alkoxy,

halogen,

haloalkyl,

loweralkyl, and

nitro,

sulphydryl,

thioxo, and

thioalkoxy,

L₅ is absent or selected from the group consisting of

(a) C₁-to-C₁₀-alkylene and

(b) C₂-to-C₁₆-alkenylene

wherein (a) and (b) are unsubstituted or substituted as

defined previously, and

R₅ is selected from the group consisting of

hydrogen,

alkanoyl wherein the alkanoyl is unsubstituted or

substituted with substituents selected from the

group consisting of aryl,

alkoxy,
alkoxyalkyl,
470 alkoxy carbonyl wherein the alkoxy carbonyl is
unsubstituted or substituted with 1, 2 or 3
substituents independently selected from the
group consisting of
aryl and
475 halogen,
alkylaminocarbonylalkyl wherein the
alkylaminocarbonylalkyl is unsubstituted or
substituted with 1 or 2 substituents
independently selected from the group consisting
480 of aryl,
(anthracenyl)alkyl,
aryl,
arylalkoxy,
arylalkyl wherein the arylalkyl is unsubstituted or
485 substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group
consisting of
alkoxy,
aryl,
490 carboxyl,
cyano,
halogen,
haloalkoxy,
haloalkyl,
495 nitro,
oxo, and
-L₁₁-C(R₁₄)(R_v)-C(O)OR₁₅,
(aryl)oyl wherein the (aryl)oyl is unsubstituted or
substituted with substituents selected from the
500 group consisting of halogen,
aryloxy carbonyl,
carboxaldehyde,
-C(O)NRR',
cycloalkoxy carbonyl,

- 505 cycloalkylaminocarbonyl,
 cycloalkylaminothiocarbonyl,
 cyanoalkyl,
 cyclolalkyl,
 cycloalkylalkyl wherein the cycloalkylalkyl is
 510 unsubstituted or substituted with 1 or 2 hydroxyl
 substituents,
 with the proviso that no two hydroxyls are attached to the
 same carbon,
 (cyclolalkyl)oyl,
 515 (9,10-dihydroanthracenyl)alkyl wherein the
 (9,10-dihydroanthracenyl)alkyl is unsubstituted
 or substituted with 1 or 2 oxo substituents,
 haloalkyl,
 heterocycle,
 520 (heterocyclic)alkyl wherein the (heterocyclic)alkyl is
 unsubstituted or substituted with 1, 2, 3, 4, or 5
 substituents selected from the group consisting of
 loweralkyl,
 (heterocyclic)oyl,
 525 loweralkyl, wherein the loweralkyl is unsubstituted
 or substituted with substituents selected from the
 group consisting of -NRR',
 -SO₂-A, and
 thioalkoxyalkyl;
 530
- (2) -L₄-O-L₅-,
- (3) -L₄-S(O)_m-L₅- wherein L₄ and L₅ are defined previously and m is 0, 1,
 or 2,
- 535 (4) -L₄-L₆-C(W)-N(R₆)-L₅- wherein L₄, W, and L₅ are defined previously,
 R₆ is selected from the group consisting of
- (a) hydrogen,
 (b) loweralkyl,
 540 (c) aryl,
 (d) arylalkyl,

- (e) heterocycle,
 (f) (heterocyclic)alkyl,
 (g) cyclolakyl, and
 545 (h) cycloalkylalkyl, and
 L_6 is absent or is selected from the group consisting of
 (a) -O-,
 (b) -S-, and
 (c) -N(R_6)- wherein R_6 is selected from the group
 550 consisting of
 hydrogen,
 loweralkyl,
 aryl,
 arylalkyl,
 555 heterocycle,
 (heterocyclic)alkyl,
 cyclolakyl, and
 cycloalkylalkyl,
- 560 (5) $-L_4-L_6-S(O)_m-N(R_5)-L_5-$,
 (6) $-L_4-L_6-N(R_5)-S(O)_m-L_5-$,
 (7) $-L_4-N(R_5)-C(W)-L_7-L_5-$ wherein L_4 , R_5 , W , and L_5 are
 565 defined previously and L_7 is absent or is selected from the group
 consisting of -O- and -S-,
 (8) C_1-C_{10} -alkylene wherein the alkylene group is unsubstituted or
 substituted with 1 or 2 substituents independently selected from
 570 the group consisting of
 (a) aryl,
 (b) arylalkyl,
 (c) heterocycle,
 (d) (heterocyclic)alkyl,
 575 (e) cyclolakyl,
 (f) cycloalkylalkyl,
 (g) alkylthioalkyl, and
 (h) hydroxy,

580 (9) C₂-to-C₁₀-alkenylene wherein the alkenylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

- (a) aryl,
- (b) arylalkyl,
- 585 (c) (aryl)oxyalkyl wherein the (aryl)oxyalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,
- (d) heterocycle,
- 590 (e) (heterocycle)alkyl,
- (f) hydroxyalkyl,
- (g) cyclolalkyl,
- (h) cycloalkylalkyl,
- (i) alkylthioalkyl, and
- 595 (j) hydroxy,

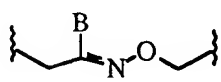
(10) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

- 600 (a) aryl,
- (b) arylalkyl,
- (c) heterocycle,
- (d) (heterocyclic)alkyl,
- (e) cyclolalkyl,
- 605 (f) cycloalkylalkyl,
- (g) alkylthioalkyl, and
- (h) hydroxy,

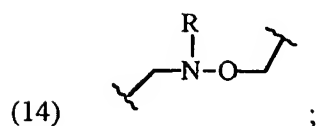
(11) -L₄-heterocycle-L₅-,

610

(12) a covalent bond,

(13)  wherein B is selected from the group consisting of loweralkyl and

615 arylalkyl, and



Z is selected from the group consisting of

- 620 (1) a covalent bond,
 (2) -O-,
 (3) -S(O)_q-, and
 (4) -NR_Z- wherein R_Z is selected from the group consisting of
 625 (a) hydrogen
 (b) loweralkyl,
 (c) aryl,
 (d) arylalkyl,
 (e) heterocycle,
 (f) (heterocyclic)alkyl,
 630 (g) cyclolalkyl, and
 (h) cycloalkylalkyl;

R₃ is selected from the group consisting of

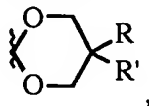
- (1) hydrogen,
 635 (2) aryl,
 (3) fluorenyl,
 (4) heterocycle,

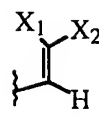
wherein (2)-(4) are unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

- 640 (a) alkanoyl,
 (b) alkoxy wherein the alkoxy is unsubstituted or substituted with 1,
 2, 3, 4, or 5 substituents independently selected from the
 group consisting of
 halogen,
 645 aryl, and
 cycloalkyl,
 (c) alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or
 substituted with 1 or 2, 3, 4 or 5 substituents
 independently selected from the group consisting of

- 650 aryl and
cycloalkyl,
- (d) alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of
655 aryl, and
cycloalkyl,
- (e) alkylsilyloxyalkyl,
- (f) arylalkyl,
- (g) aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3,
660 4, or 5 substituents independently selected from the
group consisting of
alkanoyl,
alkoxy wherein the alkoxy is unsubstituted or substituted
with 1 or 2 substituents selected from the group
665 consisting of cycloalkyl,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
670 nitro,
-NRR', and
thioalkoxy,
- (h) arylalkyl,
- (i) aryloxy wherein the aryloxy is unsubstituted or
675 substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of,
halogen,
nitro, and
-NRR',
- 680 (j) (aryl)oyl,
- (k) carboxaldehyde,
- (l) carboxy,
- (m) carboxyalkyl,
- (n) -C(O)NRR" wherein R is defined previously and R" is
685 selected from the group consisting of
hydrogen,

- loweralkyl, and
carboxyalkyl,
- 690 (o) cyano,
(p) cyanoalkyl,
(q) cycloalkyl,
(r) cycloalkylalkyl,
(s) cycloalkoxyalkyl,
(t) halogen,
- 695 (u) haloalkyl wherein the haloalkyl is unsubstituted or substituted
with 1, 2, 3, 4, or 5 hydroxyl substituents,
with the proviso that no two hydroxyls are attached to the same
carbon,
- (v) heterocycle,
- 700 (w) hydroxyl,
(x) hydroxyalkyl wherein the hydroxyalkyl is unsubstituted or
substituted with substituents selected from the group
consisting of aryl,
- (y) loweralkyl wherein the loweralkyl is unsubstituted or substituted
705 with substituents selected from the group consisting of
heterocycle,
hydroxyl,
with the proviso that no two hydroxyls are attached to the
same carbon,
- 710 -NRR³RR^{3'}, and
-P(O)(OR)(OR'),
- (z) nitro,
(aa) -NRR',
(bb) oxo,
- 715 (cc) -SO₂NR_A'R_B' wherein R_A' and R_B' are independently selected
from the group consisting of
hydrogen,
(aryl)oyl,
loweralkyl, and
- 720 heterocycle wherein the heterocycle is unsubstituted or
substituted with 1, 2, or 3 substituents
independently selected from the group consisting
of loweralkyl,

- (dd) sulfhydryl, and
 725 (ee) thioalkoxy,
- (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with
 1, 2, 3, 4 or 5 substituents selected from the group consisting of
 730 (a) alkoxy,
 (b) aryl,
 (c) arylalkoxy
 (d) aryloxy wherein the aryloxy is unsubstituted or
 substituted with 1, 2, 3, 4, or 5 substituents
 selected from the group consisting of halogen,
 735 (e) loweralkyl,
 (f) halogen,
 (g) $\text{NR}^3\text{R}^3\text{R}^3$,
 (h) oxo, and
 (i) ,
 740
- (6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted
 with 1, 2, 3 or 4 substituents independently selected from the
 group consisting of
 745 (a) loweralkyl,
 (b) alkoxy,
 (c) halogen,
 (d) aryl,
 (e) aryloxy,
 (f) alkanoyl, and
 750 (g) $\text{NR}^3\text{R}^3\text{R}^3$,

- (7)  wherein X_1 and X_2 together are cycloalkyl wherein the
 cycloalkyl is unsubstituted or substituted with 1 or 2 substituents
 selected from the group consisting of aryl, and

755

- (8) $-\text{P}(\text{W})\text{R}^3\text{R}^3\text{R}^3$; and

R₄ is selected from the group consisting of

- (1) hydrogen,
- 760 (2) loweralkyl,
- (3) haloalkyl
- (4) halogen,
- (5) aryl,
- (6) arylalkyl,
- 765 (7) heterocycle,
- (8) (heterocyclic)alkyl
- (9) alkoxy, and
- (10) -NRR'; or

770 **L₁, Z, and R₃** together are selected from the group consisting of

- (1) aminoalkyl,
- (1) haloalkyl,
- (2) halogen,
- (3) carboxaldehyde, and
- 775 (4) (carboxaldehyde)alkyl, and
- (5) hydroxyalkyl,

with the proviso that when **L₁, Z, and R₃** together are (1)-(5), **R₁** is other than hydrogen.

In a further aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with a
780 pharmaceutically acceptable carrier.

In yet another aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.

In yet another aspect of the present invention is disclosed a method for inhibiting
785 protein isoprenyl transferases (i.e., protein farnesyltransferase and/or geranylgeranyltransferase) in a human or lower mammal, comprising administering to the patient a therapeutically effective amount of a compound compound of formula I.

In yet another aspect of the present invention is disclosed a method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase,
790 protein geranylgeranyltransferase or both.

In yet another aspect of the present invention is disclosed a method for treatment of conditions mediated by farnesylated or geranylgeranylated proteins, for example, treatment of Ras associated tumors in humans and other mammals.

795 In yet another aspect of the present invention is disclosed a method for inhibiting or treating cancer in a human or lower mammal comprising administering to the patient a therapeutically effective amount of a compound of the invention alone or in combination with another chemotherapeutic agent

800 In yet another aspect of the present invention is disclosed a method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

805 The compounds of the invention can comprise asymmetrically substituted carbon atoms. As a result, all stereoisomers of the compounds of the invention are meant to be included in the invention, including racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-30, which is hereby incorporated herein by reference.

810 Detailed Description

Definitions of Terms

As used herein the terms "Cys," "Glu," "Leu," "Lys," "Met," "nor-Leu," "nor-Val," "Phe," "Ser" and "Val" refer to cysteine, glutamine, leucine, lysine, methionine, norleucine, norvaline, phenylalanine, serine and valine in their L-, D- or DL forms. As 815 used herein these amino acids are in their naturally occurring L- form.

As used herein, the term "carboxy protecting group" refers to a carboxylic acid protecting ester group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 820 152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy protecting group can be used as a prodrug whereby the carboxy protecting group can be readily cleaved *in vivo* (for example by enzymatic hydrolysis) to release the biologically active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975), which is hereby incorporated herein by 825 reference. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields (as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference). Examples of esters 830 useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21

of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press, New York (1987), which is hereby incorporated herein by reference. Representative carboxy protecting groups are C₁ to C₈ loweralkyl (e.g., methyl, ethyl or tertiary butyl and the like); arylalkyl, for example, phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-indanyl and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxy)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxyacylalkyl or cycloalkyloxyacylalkyl, such as methoxyacylmethyl, cyclohexyloxyacylmethyl, 1-methoxyacyl-1-ethyl, and the like; alkoxyacyloxyalkyl or cycloalkyloxyacyloxyalkyl, such as methoxyacyloxymethyl, t-butyloxyacyloxymethyl, 1-ethoxyacyloxy-1-ethyl, 1-cyclohexyloxyacyloxy-1-ethyl and the like; aryloxyacyloxyalkyl, such as 2-(phenoxyacyloxy)ethyl, 2-(5-indanyloxyacyloxy)ethyl and the like; alkoxyalkylcarbonyloxyalkyl, such as 2-(1-methoxy-2-methylpropan-2-oyloxy)ethyl and the like; arylalkyloxyacyloxyalkyl, such as 2-(benzyloxyacyloxy)ethyl and the like; arylalkenyloxyacyloxyalkyl, such as 2-(3-phenylpropen-2-yloxyacyloxy)ethyl and the like; alkoxyacylaminoalkyl, such as t-butyloxyacylaminoethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminoethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

Preferred carboxy-protected compounds of the invention are compounds wherein the protected carboxy group is a loweralkyl, cycloalkyl or arylalkyl ester, for example, methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, sec-butyl ester, isobutyl ester, amyl ester, isoamyl ester, octyl ester, cyclohexyl ester, phenylethyl ester and the like or an

alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl or an arylalkylcarbonyloxyalkyl ester.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated herein by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxycarbonyl, a-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, a,a-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "alkanoyl" as used herein refers to $R_{29}C(O)-$ wherein R_{29} is a loweralkyl group. The alkanoyl groups of this invention can be optionally substituted.

The term "alkanoylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{71}-NH-$ wherein R_{71} is an alkanoyl group. The alkanoylaminoalkyl groups of this invention can be optionally substituted.

The term "alkanoyloxy" as used herein refers to $R_{29}C(O)-O-$ wherein R_{29} is a loweralkyl group. The alkanoyloxy groups of this invention can be optionally substituted.

The term "alkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an alkanoyloxy group. The alkanoyloxyalkyl groups of this invention can be optionally substituted.

The term "alkenyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenyl include $-\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CH}=\text{CH}_2$, $-\text{C}(\text{CH}_3)=\text{CH}_2$, $-\text{CH}_2\text{CH}=\text{CHCH}_3$, and the like. The alkenyl groups of this invention can be optionally substituted.

The term "alkenylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 20 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenylene include $-\text{CH}=\text{CH}-$, $-\text{CH}_2\text{CH}=\text{CH}-$, $-\text{C}(\text{CH}_3)=\text{CH}-$, $-\text{CH}_2\text{CH}=\text{CHCH}_2-$, and the like. The alkenylene groups of this invention can be optionally substituted.

The term "alkenyloxy" as used herein refers to an alkenyl group attached to the parent molecular group through an oxygen atom. The alkenyloxy groups of this invention can be optionally substituted.

The term "alkenyloxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkenyloxy group. The alkenyloxyalkyl groups of this invention can be optionally substituted.

The term "alkoxy" as used herein refers to $\text{R}_{30}\text{O}-$ wherein R_{30} is loweralkyl as defined above. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy and the like. The alkoxy groups of this invention can be optionally substituted.

The term "alkoxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkoxy group. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkoxy" as used herein refers to $\text{R}_{31}\text{O}-\text{R}_{32}\text{O}-$ wherein R_{31} is loweralkyl as defined above and R_{32} is an alkylene radical. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like. The alkoxyalkoxy groups of this invention can be optionally substituted.

The term "alkoxyalkyl" as used herein refers to an alkoxy group as previously defined appended to an alkyl group as previously defined. Examples of alkoxyalkyl include, but are not limited to, methoxymethyl, methoxyethyl, isopropoxymethyl and the like. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $\text{R}_{66}-\text{C}(\text{O})-\text{O}-$ wherein R_{66} is an alkoxyalkyl group.

The term "alkoxyarylalkyl" as used herein refers to an arylalkyl group to which is attached an alkoxy group. The alkoxyarylalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonyl" as used herein refers to an alkoxy group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of

940 alkoxy carbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the like. The alkoxy carbonyl groups of this invention can be optionally substituted. The alkoxy carbonyl groups of this invention can be optionally substituted.

The term "alkoxy carbonyl alkyl" as used herein refers to an alkoxy carbonyl group as previously defined appended to a lower alkyl radical. Examples of alkoxy carbonyl alkyl
945 include methoxycarbonylmethyl, 2-ethoxycarbonylethyl and the like. The alkoxy carbonyl alkyl groups of this invention can be optionally substituted.

The term "alkoxy carbonyl amino alkyl" as used herein refers to a lower alkyl radical to which is appended $R_{69}-NH-$ wherein R_{69} is an alkoxy carbonyl group. The alkoxy carbonyl amino alkyl groups of this invention can be optionally substituted.

950 The term "alkoxy carbonyloxy alkyl" as used herein refers to a lower alkyl radical to which is appended $R_{63}-O-$ wherein R_{63} is an alkoxy carbonyl group. The alkoxy carbonyloxy alkyl groups of this invention can be optionally substituted.

The term "alkyl amino" as used herein refers to $R_{35}NH-$ wherein R_{35} is a lower alkyl group, for example, methyl amino, ethyl amino, butyl amino, and the like. The alkyl amino
955 groups of this invention can be optionally substituted.

The term "alkyl amino alkyl" as used herein refers a lower alkyl radical to which is appended an alkyl amino group. The alkyl amino alkyl groups of this invention can be optionally substituted.

The term "alkyl aminocarbonyl amino alkyl" as used herein refers to a lower alkyl
960 radical to which is appended $R_{70}-C(O)-NH-$ wherein R_{70} is an alkyl amino group. The alkyl aminocarbonyl amino alkyl groups of this invention can be optionally substituted.

The term "alkylene" as used herein refers to a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene,
965 2,2-dimethylpropylene, and the like. The alkylene groups of this invention can be optionally substituted.

The term "alkyl silyloxy" as used herein refers to a lower alkyl group to which is attached $-OSiR_W R_X R_Y$ wherein R_W , R_X , and R_Y are selected from the group consisting of lower alkyl.

970 The term "alkyl sulfinyl" as used herein refers to $R_{33}S(O)-$ wherein R_{33} is a lower alkyl group. The alkyl sulfinyl groups of this invention can be optionally substituted.

The term "alkyl sulfinyl alkyl" as used herein refers to an alkyl group to which is attached a alkyl sulfinyl group. The alkyl sulfinyl alkyl groups of this invention can be optionally substituted.

975 The term "alkyl sulfonyl" as used herein refers to $R_{34}S(O)_2-$ wherein R_{34} is a lower alkyl group. The alkyl sulfonyl groups of this invention can be optionally substituted.

The term "alkylsulfonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkylsulfonyl group. The alkylsulfonylalkyl groups of this invention can be optionally substituted.

980 The term alkylthioalkyl as used herein refers to a lower alkyl group as defined herein attached to the parent molecular moiety through a sulfur atom and an alkylene group. The alkylthioalkyl groups of this invention can be optionally substituted.

The term "alkynyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynyl include $-C\equiv CH$, $-CH_2C\equiv CH$, $-CH_2C\equiv CCH_3$, and the like.
985 The alkynyl groups of this invention can be optionally substituted.

The term "alkynylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynylene include $-C\equiv C-$,
990 $-CH_2C\equiv C-$, $-CH_2C\equiv CCH_2-$, and the like. The alkynylene groups of this invention can be optionally substituted.

The term "amino" as used herein refers to $-NH_2$.

The term "aminocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a carbonyl group. The aminocarbonyl groups of this
995 invention can be optionally substituted.

The term "aminocarbonylalkyl" as used herein refers to an alkyl group to which is attached an aminocarbonyl group. The aminocarbonylalkyl groups of this invention can be optionally substituted.

The term "aminoalkyl" as used herein refers to a loweralkyl radical to which is
1000 appended an amino group. The aminoalkyl groups of this invention can be optionally substituted.

The term "aminothiocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a thiocarbonylcarbonyl ($C=S$) group. The aminothiocarbonyl groups of this invention can be optionally substituted.

1005 The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an aryloxy group (i.e., $R_{61}-C(O)O-$ wherein R_{61} is an aryl group). The aryloxyalkyl groups of this invention can be optionally substituted.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl,
1010 tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, sulfhydryl, nitro, cyano, carboxaldehyde, carboxy,

alkoxycarbonyl, haloalkyl-C(O)-NH-, haloalkenyl-C(O)-NH- and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylalkenyl" as used herein refers to an alkenyl radical to which is appended an aryl group. The arylalkenyl groups of this invention can be optionally substituted.

The term "arylalkenyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{68}-O-C(O)-O-$ wherein R_{68} is an arylalkenyl group. The arylalkenyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "arylalkoxy" as used herein refers to an alkoxy group to which is attached an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

The term "arylalkyl" as used herein refers to a loweralkyl radical to which is appended an aryl group. Representative arylalkyl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl and the like. The arylalkyl groups of this invention can be optionally substituted.

The term "arylalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkylcarbonyloxy group (i.e., $R_{62}C(O)O-$ wherein R_{62} is an arylalkyl group). The arylalkylcarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxy" as used herein refers to an aryl group attached to the parent molecular group through an oxygen atom. The aryloxy groups of this invention can be optionally substituted.

The term "aryloxycarbonyl" as used herein refers to an aryloxy group attached to the parent molecular group through a carbonyl group. The aryloxycarbonyl groups of this invention can be optionally substituted.

The term "aryloyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The aryloyl groups of this invention can be optionally substituted.

The term "arylalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{67}-O-C(O)-O-$ wherein R_{67} is an arylalkyl group. The arylalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{65}-O-$ wherein R_{65} is an aryl group. The aryloxyalkyl groups of this invention can be optionally substituted.

The term "arylalkoxy" as used herein refers to an alkoxy radical to which is appended $R_{65}-O-$ wherein R_{65} is an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

1050 The term "arylalkyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkoxy group. The arylalkyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxy" as used herein refers to $R_{65}-O-$ wherein R_{65} is an aryl group. The aryloxy groups of this invention can be optionally substituted. The aryloxy groups of
1055 this invention can be optionally substituted.

The term "(aryl)oyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The (aryl)oyl groups of this invention can be optionally substituted.

The term "aryloxythioalkoxyalkyl" as used herein refers to a loweralkyl radical to
1060 which is appended $R_{75}-S-$ wherein R_{75} is an aryloxyalkyl group. The aryloxythioalkoxyalkyl groups of this invention can be optionally substituted.

The term "aryloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{65}-O-C(O)-O-$ wherein R_{65} is an aryl group. The
aryloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

1065 The term "arylsulfonyl" as used herein refers to $R_{36}S(O)_2-$ wherein R_{36} is an aryl group. The arylsulfonyl groups of this invention can be optionally substituted.

The term "arylsulfonyloxy" as used herein refers to $R_{37}S(O)_2O-$ wherein R_{37} is an aryl group. The arylsulfonyloxy groups of this invention can be optionally substituted.

The term "carboxy" as used herein refers to $-COOH$.

1070 The term "carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxy ($-COOH$) group. The carboxyalkyl groups of this invention can be optionally substituted.

The term "cyanoalkyl" as used herein used herein refers to a loweralkyl radical to which is appended a cyano ($-CN$) group. The cyanoalkyl groups of this invention can be
1075 optionally substituted.

The term "carboxaldehyde" as used herein used herein refers to $-CHO$.

The term "(carboxaldehyde)alkyl" as used herein used herein refers to a carboxaldehyde group attached to a loweralkyl group. The (carboxaldehyde)alkyl groups of this invention can be optionally substituted.

1080 The terms "cycloalkanoyl" and "(cycloalkyl)oyl" refer to a cycloalkyl group attached to the parent molecular group through a carbonyl group. The cycloalkanoyl and (cycloalkyl)oyl groups of this invention can be optionally substituted.

The term "cycloalkanoylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkanoyl group (i.e., $R_{60}-C(O)-$ wherein R_{60} is a cycloalkyl group).

1085 The cycloalkanoylalkyl groups of this invention can be optionally substituted.

The term "cycloalkylalkoxyalkyl" as used herein refers to an alkoxyalkyl group to which is attached a cycloalkyl group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

1090 The term "cycloalkenyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms and containing a carbon-carbon double bond including, but not limited to, cyclopentenyl, cyclohexenyl and the like. The cycloalkenyl groups of this invention can be optionally substituted.

1095 The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through an oxygen atom. The cycloalkoxy groups of this invention can be optionally substituted.

The term "cycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a cycloalkoxy group. The cycloalkoxyalkyl groups of this invention can be optionally substituted.

1100 The term "cycloalkoxycarbonyl" as used herein refers to a cycloalkoxy group attached to the parent molecular group through a carbonyl group. The cycloalkoxycarbonyl groups of this invention can be optionally substituted.

1105 The term "cycloalkyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl and the like. The cycloalkyl groups of this invention can be optionally substituted. The cycloalkyl groups of this invention can be optionally substituted.

The term "cycloalkylaminocarbonyl" as used herein refers to $\text{NHR}_{60}\text{C}(\text{O})-$ wherein R_{60} is a cycloalkyl group. The cycloalkylaminocarbonyl groups of this invention can be optionally substituted.

1110 The term "cycloalkylaminothiocarbonyl" as used herein refers to $\text{NHR}_{60}\text{C}(\text{S})-$ wherein R_{60} is defined above. The cycloalkylaminothiocarbonyl groups of this invention can be optionally substituted.

1115 The term "cycloalkylalkoxy" as used herein refers to an alkoxy radical to which is appended a cycloalkyl group. The cycloalkylalkoxy groups of this invention can be optionally substituted.

The term "cycloalkylalkoxyalkyl" as used herein refers to an alkyl radical to which is appended a cycloalkylalkoxy group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

1120 The term "cycloalkylalkoxycarbonyl" as used herein refers to a cycloalkylalkoxy radical attached to the parent molecular group through a carbonyl group. The cycloalkylalkoxycarbonyl groups of this invention can be optionally substituted.

The term "cycloalkylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkyl group. Representative examples of cycloalkylalkyl include cyclopropylmethyl, cyclohexylmethyl, 2-(cyclopropyl)ethyl, adamantylmethyl and the like.

1125 The cycloalkylalkyl groups of this invention can be optionally substituted.

The term "cycloalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{64}-O-C(O)-O-$ wherein R_{64} is a cycloalkyl group. The cycloalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

1130 The term "dialkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two alkoxy groups. The dialkoxyalkyl groups of this invention can be optionally substituted.

1135 The term "dialkylamino" as used herein refers to $R_{38}R_{39}N-$ wherein R_{38} and R_{39} are independently selected from loweralkyl, for example dimethylamino, diethylamino, methyl propylamino, and the like. The dialkylamino groups of this invention can be optionally substituted.

The term "dialkylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended a dialkylamino group. The dialkylaminoalkyl groups of this invention can be optionally substituted.

1140 The term "dialkylaminocarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{73}-C(O)-$ wherein R_{73} is a dialkylamino group. The dialkylaminocarbonylalkyl groups of this invention can be optionally substituted.

The term "dioxoalkyl" as used herein refers to a loweralkyl radical which is substituted with two oxo ($=O$) groups. The dioxoalkyl groups of this invention can be optionally substituted.

1145 The term "dithioalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two thioalkoxy groups. The dithioalkoxyalkyl groups of this invention can be optionally substituted.

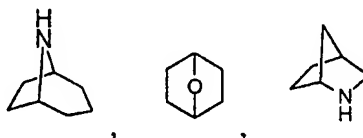
The term "halogen" or "halo" as used herein refers to I, Br, Cl or F.

1150 The term "haloalkenyl" as used herein refers to an alkenyl radical, as defined above, bearing at least one halogen substituent. The haloalkenyl groups of this invention can be optionally substituted.

1155 The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like. Haloalkyl can also include perfluoroalkyl wherein all hydrogens of a loweralkyl group are replaced with fluorides.

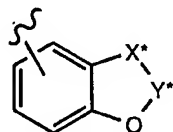
The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to a 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur or a 5-membered ring

containing 4 nitrogen atoms; and includes a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one oxygen and one sulfur atom in non-adjacent positions; two sulfur atoms in non-adjacent positions; two sulfur atoms in adjacent positions and one nitrogen atom; two adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one oxygen atom. The 5-membered ring has 0-2 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The term "heterocyclic" also includes bicyclic, tricyclic and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from the group consisting of an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring and another monocyclic heterocyclic ring (for example, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl or benzothienyl and the like). Heterocyclics include: pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyrimidyl, tetrahydrofuryl, dihydrofuryl, tetrahydrothienyl, dihydrothienyl, dihydroindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, pyranyl, dihydropyranyl, dithiazolyl, benzofuryl and benzothienyl. Heterocyclics also include bridged bicyclic groups wherein a monocyclic heterocyclic group is bridged by an alkylene group, for example,



and the like.

Heterocyclics also include compounds of the formula



wherein X* is -CH₂-, -CH₂O- or -O- and Y* is -C(O)- or -(C(R''))_v - wherein R'' is hydrogen or C₁-C₄-alkyl and v is 1, 2 or 3 such as 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like.

1190 Heterocyclics can be unsubstituted or substituted with one, two, three, four or five substituents independently selected from the group consisting of

a) hydroxy, b) -SH, c) halo, d) oxo (=O), e) thioxo (=S), f) amino, g) -NHOH, h) alkylamino, i) dialkylamino, j) alkoxy, k) alkoxyalkoxy, l) haloalkyl, m) hydroxyalkyl, n) alkoxyalkyl, o) cycloalkyl which is unsubstituted or substituted with one, two, three or four

1195 loweralkyl groups, p) cycloalkenyl which is unsubstituted or substituted with one, two, three or four loweralkyl groups, q) alkenyl, r) alkynyl, s) aryl, t) arylalkyl, u) -COOH, v) -SO₃H, w) loweralkyl, x) alkoxycarbonyl, y) -C(O)NH₂, z) -C(S)NH₂, aa) -C(=N-OH)NH₂, bb) aryl-L₁₆-C(O)- wherein L₁₆ is an alkenylene radical, cc) -S-L₁₇-C(O)OR₄₀ wherein L₁₇ is an alkylene radical which is unsubstituted or substituted with one or two

1200 substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₂ is loweralkyl) and R₄₀ is hydrogen or a carboxy-protecting group, dd) -S-L₁₈-C(O)NR₄₃R₄₄ wherein L₁₈ is an alkylene radical which is unsubstituted or substituted with one or two

1205 substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₃ and R₄₄ are independently selected from the group consisting of hydrogen, loweralkyl and aryl, ee) -S-L₁₉-CN wherein L₁₉ is an alkylene radical, ff) -S-L₂₀-R₄₅ wherein L₂₀ is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with oxo (=O) and R₄₅ is

1210 hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, gg) -O-L₂₁-R₄₆ wherein L₂₁ is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the

1215 alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₆ is hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group

1220 consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, hh) -O-S(O)₂-R₄₇ wherein R₄₇ is aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, ii) -S(O)₂-NH-R₄₈ wherein R₄₈ is

1225 aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or

substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, jj) alkylsulfinyl, kk) alkylsulfonyl, ll) arylsulfonyl, mm) arylsulfonyloxy, nn) $-C(=NOR_{49})C(O)OR_{50}$ wherein R_{49} is hydrogen or loweralkyl and R_{50} is hydrogen or a carboxy-protecting group, oo) alkoxycarbonylalkyl, pp) carboxyalkyl, qq) cyanoalkyl, rr) alkylaminoalkyl, ss) N-protected alkylaminoalkyl, tt) dialkylaminoalkyl, uu) dioxoalkyl, vv) loweralkyl-C(O)-, ww) loweralkyl-C(S)-, xx) aryl-C(O)-, yy) aryl-C(S)-, zz) loweralkyl-C(O)-O-, aaa) loweralkyl-S-C(S)- bbb) N-protected amino, ccc) aminoalkyl-C(O)-, ddd) N-protected aminoalkyl-C(O)- eee) aminoalkyl-C(S)-, fff) N-protected aminoalkyl-C(S)-, ggg) aminoalkyl, hhh) N-protected aminoalkyl, iii) formyl, jjj) cyano, kkk) nitro, lll) spiroalkyl, mmm) oxoalkyloxy, nnn) $R_{53}-L_{22}-$, wherein L_{22} is alkenylene or alkynylene and R_{53} is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, ooo) aryl-NH-C(O)-, ppp) $R_{54}-N=N-$ wherein R_{54} is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, qqq) $=N-R_{55}$ wherein R_{55} is hydrogen, aryl, heterocyclic, $-S(O)_2$ -aryl or $-S(O)_2$ -heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, rrr) diarylalkyl-N=N-, sss) aryl-N(R_{56})- or arylalkyl-N(R_{56})- wherein R_{56} is hydrogen or an N-protecting group, ttt) aryl-sulfonylalkyl, uuu) heterocyclicsulfonylalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, vvv) $=C(CN)(C(O)NH_2)$, www) $=C(CN)(C(O)O$ -loweralkyl), xxx) heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, yyy) hydroxythioalkoxy, zzz) aryloxyalkyl, aaaa) aryloxyalkylthioalkoxy, bbbb) dialkoxyalkyl, cccc) dithioalkoxyalkyl, dddd) arylalkyl-NH- L_{23} - wherein L_{23} is an alkylene group, eeee) heterocyclicalkyl-NH- L_{24} - wherein L_{24} is an alkylene group, ffff) aryl-S(O) $_2$ -NH- L_{25} - wherein L_{25} is an alkylene group, gggg) heterocyclic-S(O) $_2$ -NH- L_{26} - wherein L_{26} is an alkylene group, hhhh) aryl-C(O)-NH- L_{27} - wherein L_{27} is an alkylene group and iiiii) heterocyclic-C(O)-NH- L_{28} -

wherein L_{28} is an alkylene group, $ijij$) $R_{yy}(CH_2)_n-X-Y-Z-(CH_2)_m$ wherein R_{yy} is
1265 cycloalkyl, aryl and loweralkyl, n and m are independently 0-2, Z is O or absent, Y is
absent, CH_2 , $CHOH$ or $C(O)$, with the proviso that when X is O, Z is absent and with the
proviso that when Z is O, X is absent and with the proviso that when Y is $CHOH$, X and Z
are absent.

The term "(heterocyclic)alkoxy" as used herein refers to an alkoxy group to which is
1270 attached a heterocycle. The (heterocyclic)alkoxy groups of this invention can be optionally
substituted.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as
defined above appended to a loweralkyl radical as defined above. Examples of heterocyclic
alkyl include 2-pyridylmethyl, 4-pyridylmethyl, 4-quinolinylmethyl and the like. The
1275 (heterocyclic)alkyl groups of this invention can be optionally substituted.

The term "(heterocyclic)oxy" as used herein refers to a heterocycle connected to the
parent molecular group through an oxygen atom. The (heterocyclic)oxy groups of this
invention can be optionally substituted.

The term "(heterocyclic)oxyalkyl" as used herein refers to a loweralkyl group to which is
1280 attached a (heterocyclic)oxy group. The (heterocyclic)oxyalkyl groups of this invention can
be optionally substituted.

The term "(heterocyclic)alkoxyalkyl" as used herein refers to an alkoxyalkyl group
to which is attached a heterocycle. The (heterocyclic)alkoxyalkyl groups of this invention
can be optionally substituted.

1285 The term "heterocycliccarbonyloxyalkyl" as used herein refers to a loweralkyl radical
to which is appended $R_{72}-C(O)-O-$ wherein R_{72} is a heterocyclic group. The
heterocycliccarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "hydroxy" as used herein refers to $-OH$.

The term "hydroxyalkyl" as used herein refers to a loweralkyl radical to which is
1290 appended an hydroxy group. The hydroxyalkyl groups of this invention can be optionally
substituted.

The term "hydroxyarylalkyl" as used herein refers to an arylalkyl group to which is
appended a hydroxy group. The hydroxyarylalkyl groups of this invention can be
optionally substituted.

1295 The term "hydroxythioalkoxy" as used herein refers to $R_{51}S-$ wherein R_{51} is a
hydroxyalkyl group. The hydroxythioalkoxy groups of this invention can be optionally
substituted.

The term "loweralkyl" as used herein refers to branched or straight chain alkyl
groups comprising one to ten carbon atoms, including methyl, ethyl, propyl, isopropyl, n -

1300 butyl, t-butyl, neopentyl and the like. The loweralkyl groups of this invention can be optionally substituted.

The term "N-protected alkylaminoalkyl" as used herein refers to an alkylaminoalkyl group wherein the nitrogen is N-protected. The N-protected alkylaminoalkyl groups of this invention can be optionally substituted.

1305 The term "nitro" as used herein refers to $-\text{NO}_2$.

The term "oxo" as used herein refers to $(=\text{O})$.

The term "oxoalkyloxy" as used herein refers to an alkoxy radical wherein the loweralkyl moiety is substituted with an oxo $(=\text{O})$ group. The oxoalkyloxy groups of this invention can be optionally substituted.

1310 The term "oxyamino(alkyl)carbonylalkyl" as used herein refers to a $-\text{O}-\text{NR}-\text{C}(\text{O})-\text{R}'$ group wherein R and R' are loweralkyl.

The term "oxyamino(arylalkyl)carbonylalkyl" as used herein refers to a $-\text{O}-\text{NR}^{\text{R}_3}-\text{C}(\text{O})-\text{R}$ group wherein R^{R_3} is arylalkyl and R is loweralkyl.

1315 The term "oxyaminocarbonylalkyl" as used herein refers to $-\text{O}-\text{NH}-\text{C}(\text{O})-\text{R}$ group wherein R is loweralkyl.

The term "spiroalkyl" as used herein refers to an alkylene diradical, both ends of which are bonded to the same carbon atom of the parent group to form a spirocyclic group. The spiroalkyl groups of this invention can be optionally substituted.

The term "sulfhydryl" as used herein refers to $-\text{SH}$.

1320 The term "sulfhydrylalkyl" as used herein refers to a loweralkyl group to which is attached a sulfhydryl group. The sulfhydrylalkyl groups of this invention can be optionally substituted.

The term "thioalkoxy" as used herein refers to $\text{R}_{52}\text{S}-$ wherein R_{52} is loweralkyl. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like.

1325 The thioalkoxy groups of this invention can be optionally substituted.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group as previously defined appended to a loweralkyl group as previously defined. Examples of thioalkoxyalkyl include thiomethoxymethyl, 2-thiomethoxyethyl and the like. The thioalkoxyalkyl groups of this invention can be optionally substituted.

1330 The term "thiocycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through a sulfur atom. The thiocycloalkoxy groups of this invention can be optionally substituted.

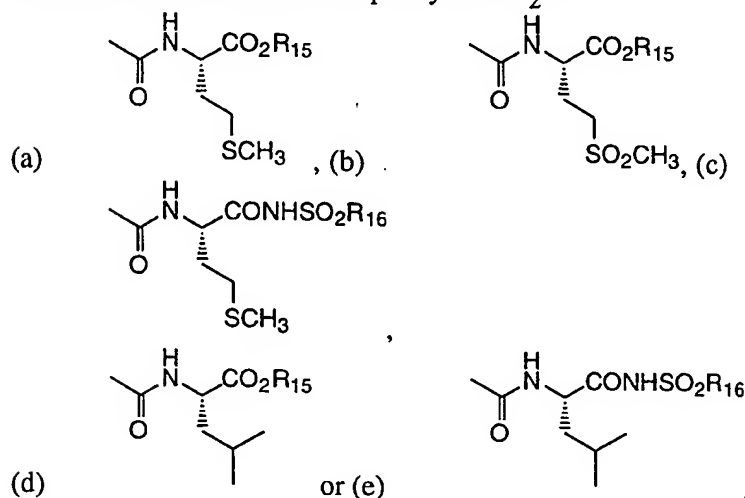
1335 The term "thiocycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a thiocycloalkoxy group. The thiocycloalkoxyalkyl groups of this invention can be optionally substituted.

Preferred embodiments

Preferred compounds of the invention are compounds of formula I wherein R_1 is unsubstituted or substituted phenyl and R_2 is $-C(O)NH-CH(R_{14})-C(O)OR_{15}$ or $-C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16}$ wherein R_2 , R_{14} , R_{15} and R_{16} are defined above.

1340

More preferred compounds of the invention are compounds of formula I wherein R_1 is unsubstituted or substituted phenyl and R_2 is

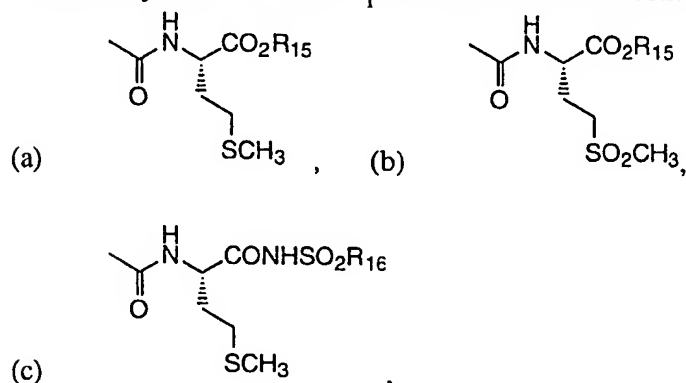


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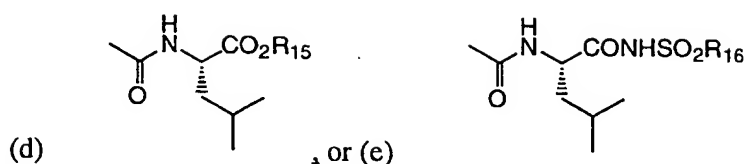
Still more preferred compounds have formula I wherein R_3 is selected from the group consisting of (a) pyridyl, (b) imidazolyl, and (c) furyl wherein the pyridyl, imidazolyl, or furyl group may be substituted with 1, 2 or 3 substituents selected from the group consisting of aryl, loweralkyl, halo, nitro, haloalkyl, hydroxy, hydroxyalkyl, amino, N-protected amino, alkoxy, and thioalkoxy.

1350

Still more preferred compounds of the invention have the structure defined immediately above wherein R_1 is unsubstituted or substituted phenyl and R_2 is



1355



1360 The most preferred compounds have the structure defined immediately above wherein R₃ is unsubstituted or substituted pyridyl or imidazolyl.

Protein Farnesyltransferase Inhibition

1365 The ability of the compounds of the invention to inhibit protein farnesyltransferase or protein geranylgeranyltransferase can be measured according to the method of Moores, et al., J. Biol. Chem. 266: 14603 (1991) or the method of Vogt, et al., J. Biol. Chem. 270:660-664 (1995). In addition, procedures for determination of the inhibition of farnesylation of the oncogene protein Ras are described by Goldstein, et al., J. Biol. Chem., 266:15575-15578 (1991) and by Singh in United States Patent No. 5,245,061.

1370 In addition, *in vitro* inhibition of protein farnesyltransferase may be measured by the following procedure. Rat brain protein farnesyltransferase activity is measured using an Amersham Life Science commercial scintillation proximity assay kit and substituting a biotin-K Ras B fragment (biotin-Lys-Lys-Ser-Lys-Thr-Lys-Cys-Val-Ile-Met-CO₂H), 0.1 mM final concentration, for the biotin-lamin substrate provided by Amersham. The enzyme is purified according to Reiss, Y., et al., Cell, 62: 81-88 (1990), utilizing steps one through three. The specific activity of the enzyme is approximately 10 nmol substrate farnesylated/mg enzyme/hour. The percent inhibition of the farnesylation caused by the compounds of the invention (at 10 x 10⁻⁶ M) compared to an uninhibited control sample is evaluated in the same Amersham test system.

1380 The % inhibition of protein farnesyltransferase was determined for representative compounds of the invention. The results are summarized in Table 1.

Tables 1-5

In Vitro Potencies of Representative Compounds

1385 Table 1. Inhibition of farnesyltransferase

% inhibition Example at 1X10 ⁻⁵ M		% inhibition Example at 1X10 ⁻⁵ M	
200	93	674	40
350	53	676	76
351	82	678	73
352	52	680	58
353	62	683	57
354	47	684	48
355	43	685	55
356	58	686	48
357	56	687	78
358	45	688	71
359	36	689	73
360	88	690	61
361	97	692	74
362	83	699	74
363	96	700	68
364	69	701	64
365	97	702	79
366	83	704	67
367	81	705	72
368	71	706	53
369	87	707	66
370	86	708	76
371	66	709	55
372	69	710	45
373	76	711	46
374	61	712	69
375	68	713	40
376	80	714	56
377	71	715	67
378	54	717	75

380	45	718	40
381	79	750	44
382	> 50	752	58
383	> 50	753	55
387	> 50	754	40
388	> 50	755	44
390	> 50	756	47
639	44	757	58
659	55	758	46
663	43	759	49
664	75	952	> 50
669	52	955	50
670	78	974	> 50
672	48		

Table 2. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-6} M	Example	% inhibition at 1×10^{-6} M
157	92	583	98
158	2	587	97
159	84	595	97
160	30	607	96
161	54	610	94
162	12	613	97
163	18	617	99
164	92	620	98
165	74	626	61
166	97	627	85
167	98	632	43
168	92	633	32
183	98	636	72
184	36	641	34
185	93	642	48
186	86	644	54
187	68	386	> 50
188	40	399	> 50
189	88	403	99
190	4	404	98
191	28	405	98
192	95	406	95
193	4	407	98
196	43	435	96
197	1	451	85
201	63	452	96
202	31	453	90
203	76	456	81
204	98	457	92
205	98	460	88
206	67	463	91
207	98	465	92
208	98	466	93

209	74	467	97
210	5	468	96
211	98	469	92
212	12	470	95
213	98	471	94
214	97	472	97
215	82	473	96
216	67	474	92
217	99	475	21
218	89	476	91
219	56	477	98
220	92	478	98
221	55	479	95
222	41	480	87
223	63	481	95
224	41	488	41
225	93	494	96
226	23	495	95
227	94	496	93
228	39	497	94
231	50	498	98
233	65	499	98
234	4	500	98
235	95	501	84
237	98	502	24
238	22	503	57
239	97	504	90
240	98	505	72
241	41	507	95
242	99	507	96
243	23	508	95
244	21	509	77
245	50	510	84
248	79	512	94
249	77	513	96
250	96	514	94

252	98	515	72
253	99	516	95
254	96	525	99
255	98	528	99
256	98	529	99
257	98	530	94
258	98	537	97
259	98	540	40
260	98	645	37
261	98	646	58
262	98	649	86
263	99	650	68
264	98	651	33
265	98	652	41
266	97	653	62
267	96	655	35
268	98	657	32
269	98	658	73
270	98	661	45
271	84	662	68
272	96	665	55
273	96	666	82
274	94	667	83
276	98	671	36
277	98	673	59
278	99	677	37
279	99	682	31
280	98	691	34
281	98	693	53
282	76	694	45
283	98	696	57
284	83	697	39
286	84	703	40
287	24	716	69
288	22	719	90
289	23	720	70

290	74	721	83
291	23	722	96
292	36	723	87
294	98	724	87
295	94	725	78
296	89	726	81
297	65	727	95
298	43	744	84
299	94	749	84
300	22	751	32
301	98	764	88
302	31	765	76
304	99	768	67
305	99	771	72
306	99	772	79
307	82	773	41
308	62	774	48
309	98	775	32
310	98	776	36
311	97	777	83
313	94	782	96
314	97	786	34
315	93	787	70
316	63	788	44
317	54	789	86
318	98	790	88
319	98	791	53
320	93	792	88
321	90	793	94
322	98	794	92
323	98	796	35
324	98	797	35
325	99	806	72
326	91	807	90
327	97	808	88
328	96	809	78

329	98	810	89
330	98	812	94
331	98	813	95
332	26	816	87
333	99	824	90
334	93	831	92
343	72	832	80
344	95	834	55
345	91	835	96
346	98	844	92
347	95	846	85
348	66	850	90
349	99	862	95
379	21	866	62
541	37	867	71
542	67	868	89
544	35	872	74
545	88	878	95
546	97	879	95
547	91	886	35
550	96	889	95
	78	902	85
728			
552	88	903	78
553	92	908	88
554	96	910	42
555	85	911	65
556	99	918	97
557	93	923	78
560	91	924	77
561	91	925	87
564	98	926	69
565	94	936	
			69
566	98	937	95
568	93	962	> 50

569	91	964	> 50
572	91	979	26
575	70	982	64
576	88	987	93
577	94	988	92
582	99	989	88

1390

Table 3. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-7} M	Example	% inhibition at 1×10^{-7} M
434	93	623	96
436	89	729	73
437	89	730	96
438	90	731	65
439	80	732	84
440	92	733	60
441	91	734	49
442	88	735	96
443	97	736	96
444	95	737	95
445	94	738	54
446	91	739	83
447	91	740	94
448	92	741	89
449	91	742	87
450	96	743	51
455	83	745	93
458	87	746	84
459	92	747	68
461	93	748	56
462	91	769	90
464	86	770	91
482	96	781	91
483	95	785	96
484	97	795	87
485	96	798	95
486	97	799	96
487	81	800	74
489	86	801	87
490	70	802	88
491	94	811	85
492	95	814	81
493	51	815	71

511	82	817	60
519	89	818	78
520	97	822	93
521	94	823	75
522	93	825	79
523	97	839	63
524	99	849	66
526	96	854	78
527	97	855	92
531	74	856	97
532	88	857	92
533	91	859	86
534	84	861	65
535	89	863	72
536	79	864	84
539	89	865	95
548	86	869	92
549	98	874	90
551	93	875	92
558	87	876	92
559	96	891	94
562	95	893	87
563	95	894	89
570	92	895	92
571	88	896	96
573	72	900	95
574	81	906	88
578	90	912	85
579	92	913	89
580	90	914	91
581	96	917	78
584	96	919	91
585	96	921	82
589	91	929	81
590	95	931	98
592	93	933	91

593	86	935	72
594	95	940	92
597	75	941	90
600	93	945	80
601	92	947	79
602	97	948	75
604	86	949	57
609	95	950	71
611	95	951	71
615	94	959	> 50
616	95	983	66
618	89	984	86
621	98	990	84
622	95	993	90

Table 4. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-8} M	Example	% inhibition at 1×10^{-8} M
384	91	851	82
397	50	852	79
398	> 50	853	85
400	98	858	60
401	66	860	85
408	> 95	870	91
409	84	871	94
410	94	873	97
517	92	877	68
518	90	880	95
567	69	881	69
586	90	882	79
588	68	883	91
591	82	884	94
599	86	885	95
603	94	887	92
605	68	888	86
606	93	892	59
608	91	897	76
612	96	898	82
614	92	899	88
619	95	901	84
760	95	904	85
762	84	905	86
763	92	907	79
766	95	909	79
767	97	916	96
779	70	920	96
780	71	922	96
803	95	927	74
804	95	928	84
805	96	930	66
819	76	932	60

820	66	934	71
821	75	938	61
826	92	939	72
827	77	942	58
828	87	943	79
829	92	944	88
833	78	946	52
836	95	954	> 50
837	91	958	> 50
838	92	960	> 50
840	73	985	89
841	93	986	95
842	88	991	69
843	96	992	93
845	85	994	83
847	85	995	92
848	87	996	80

Table 5. Inhibition of geranylgeranyltransferase I.

Example	Activity
387	> 50% inhibition at 1×10^{-6} M
388	> 50% inhibition at 1×10^{-7} M
389	> 50% inhibition at 1×10^{-6} M
390	> 50% inhibition at 1×10^{-5} M
392	> 50% inhibition at 1×10^{-5} M
399	> 50% inhibition at 1×10^{-6} M
953	> 50% inhibition at 1×10^{-6} M
955	> 50% inhibition at 1×10^{-7} M
962	> 50% inhibition at 1×10^{-7} M
964	> 50% inhibition at 1×10^{-6} M
966	> 50% inhibition at 1×10^{-6} M
967	> 50% inhibition at 1×10^{-6} M
969	> 50% inhibition at 1×10^{-5} M
974	> 50% inhibition at 1×10^{-5} M

1395

Table 6. Inhibition of farnesyltransferase at concentrations of 10 mM and 1 mM unless specified as * (0.1 mM) or ** (0.01 mM)

Example	% inhibition 10 mM	% inhibition 1 mM	Example	% inhibition 10 mM	% inhibition 1 mM
997		91**	1199		71
998		79**	1200		97*
999		90	1201		73*
1000		82*	1202		96**
1001		92**	1203		84*
1002		82**	1204		93*
1003		92*	1205		55**
1004		92**	1206		63**
1005		95**	1207		91*
1006		95**	1208		89*
1007		85**	1209		87*
1008		95**	1210		64**
1009		86**	1211		94
1010		90*	1212		86*

1011		92**	1213		79**
1012		88*	1214		92**
1013		80*	1215		17
1014		91	1216		88**
1015		59*	1217		87*
1016		92*	1218		54**
1017		51*	1219		85**
1018		97	1220		
1019		70	1221		82**
1020		39	1222		89*
1021		93*	1223		91**
1022		91**	1224		88*
1023		89**	1225		92**
1024		89**	1226		69**
1025		91**	1227		91
1026		74**	1228		88*
1027		81**	1229		66**
1028		92**	1230		77**
1029		82**	1231		93*
1030		92**	1232		68**
1031		90**	1233		77**
1032		93**	1234		71**
1033		76**	1235		86**
1034		77	1236		83**
1035		76	1237		89**
1036		79	1238		91**
1037		88	1239		85*
1038		57	1240		64**
1039		89**	1241		74*
1040		90**	1242		75*
1041		48	1243		95*
1042		88	1244		84
1043		90*	1245		92
1044		76*	1246		82

1045		86*	1247		95*
1046		93	1248		88
1047		95	1249		89
1048		78**	1250		79**
1049		93**	1251		91**
1050		62**	1252		84*
1051		79**	1253		76*
1052		91**	1254		67
1053		60**	1255		82*
1054		89**	1256		95*
1055		85**	1257		93**
1056		75**	1258		97**
1057		82*	1259		89**
1058		89	1260		90**
1059		92*	1261		94
1060		42	1262		95
1061		88*	1263		85*
1062		93	1264		83**
1063		92**	1265		90
1064		95**	1266		85*
1065		78*	1267		96
1066		73**	1268		95*
1067		93*	1269		84**
1068		79**	1270		91**
1069		74*	1271		78**
1070		93**	1272		73**
1071		95*	1273		94*
1072		82*	1274		89*
1073		93**	1275		86**
1074		82	1276		88**
1075		90**	1277		90**
1076		69**	1278		68
1077		93**	1279		87**
1078		86*	1280		78**

1079		90	1281		81*
1080		87	1282		69*
1081		61	1283		74*
1082		84*	1284		86
1083		88	1285		94
1084		76**	1286		85**
1085		93*	1287		95**
1086		87*	1288		69*
1087		76*	1289		93
1088		73*	1290		80
1089		86*	1291		
1090		81**	1292		
1091		87*	1293		
1092		74**	1294		
1093		95**	1295		
1094		96**	1296		
1095		76*	1297		
1096		86*	1298		97**
1097		80**	1299		96**
1098		60*	1300		97*
1099		87**	1301		97*
1100		82**	1302		93**
1101		86*	1303		91**
1102		84**	1304		90**
1103		92*	1305		91**
1104		89**	1306		85**
1105		91**	1307		85**
1106		67**	1308		91**
1107		88**	1309		96*
1108		95**	1310		90**
1109		74**	1311		95**
1110			1312		91**
1111		63**	1313		91**
1112		62	1314		96*

1113		55	1315		86*
1114		83**	1316		78*
1115		94*	1317	99	96
1116		91**	1318		
1117		92*	1319		79**
1118		86*	1320		79
1119		84**	1321		
1120		93	1322		
1121		72*	1323		
1122		92**	1324		
1123		90*	1325		
1124		90*	1326		
1125		92*	1327		
1126		87	1328		
1127		90*	1329		
1128		86*	1330		
1129		92**	1331		
1130		88**	1332		92**
1131		96**	1333		95*
1132		97*	1334		72**
1133		75*	1335		90*
1134		95**	1336		74
1135		88*	1337		83**
1136		91	1338		65*
1137		83**	1339		
1138		65*	1340		77*
1139		92*	1341		89
1140		77**	1342		
1141		80*	1343		88
1142		84**	1344		93**
1143		92*	1345		94**
1144		76*	1346		94*
1145		83*	1347		81**
1146		61**	1348		78**

1147		93*	1349		92**
1148		79**	1350		
1149		94*	1351		
1150		92*	1352		
1151		91*	1353		
1152		96*	1354		38
1153		89*	1355		46
1154		93*	1356		80
1155		91*	1357		78
1156		87	1358		
1157		66**	1359		
1158	75		1360		98**
1159		72*	1361		96*
1160		83*	1362		83**
1161		87*	1363		88**
1162		84*	1364		
1163		73**	1365		
1164		94	1366		79*
1165		84*	1367		93*
1166		74**	1368		92**
1167		91*	1369		94*
1168		88*	1370		86**
1169		77	1371		94*
1170		74*	1372		95**
1171		74**	1373		95**
1172		38*	1374		93**
1173		89**	1375		80**
1174		79**	1376		86**
1175		96	1377		95*
1176		97*	1378		68
1177		19	1379		41
1178		88**	1380		87**
1179		85*	1381		65**
1180		93*	1382		86**

1181		82*	1383		88*
1182		92**	1384		69**
1183		79**	1385		93*
1184		84**	1386		88*
1185		85**	1387		82**
1186		93**	1392		93*
1187		93**	1397		87**
1188		93**	1398		81*
1189		74**	1399		94
1190		95**	1400		95
1191		85**			
1192		91*			
1193		95**			
1194		78**			
1195		94*			
1196		87*			
1197		85*			
1198		86*			

* % inhibition at 0.1 μ M

** % inhibition at 0.01 μ M

1400

Additional methods for the measurement of *in vitro* inhibition of protein prenylation (i.e., inhibition of farnesyltransferase or geranylgeranyltransferase) are described below.

Assays are performed using the glass fiber filter binding assay procedure with either rabbit reticulocyte lysate or FTase or GGTase I fractions isolated from bovine brains using a combination of hydrophobic and DEAE column chromatography procedures. Protein substrates are purchased from Panvera Corporation (H-ras for FTase, H-ras-CVLL for GGTase I). Tritium labeled prenyl lipid substrates (FPP or GGPP) are obtained from Amersham Life Science.

1410

FTase

³H-Farnesyl diphosphate (final concentration 0.6 μ M), H-Ras (final concentration 5.0 μ M) and the test compound (various final concentrations from a stock solution in 50% DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50 mM HEPES (pH 7.5), 30 mM MgCl₂, 20 mM KCl, 10 μ M ZnCl₂, 5 mM DTT, 0.01% Triton X-100) to give

1415 a final volume of 50 μ L. The mixture was brought to 37 °C, enzyme was added, and the reaction is incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the reaction, and the mixture was allowed to stand for 15 minutes at room temperature then diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass
1420 filter was transferred to a scintillation vial and 5 mL of scintillation fluid was added. The radioisotope retained on the glass fiber filter was counted to reflect the activity of the enzymes. The IC₅₀ value was calculated by measuring the activity of the enzyme over a suitable range of inhibitor concentrations.

1425 GGTase I

³H-geranylgeranyldiphosphate (final concentration 0.5 μ M), H-Ras-CVLL (final concentration 5.0 μ M) and the test compound (various final concentrations from a stock solution in 1:1 DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50 mM Tris-HCl (pH 7.2), 30 mM MgCl₂, 20 mM KCl, 10 μ M ZnCl₂, 5 mM DTT, 0.01%
1430 Triton X-100) to give a final volume of 50 μ L. The mixture was brought to 37 °C, treated with enzyme, and incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the reaction, and the mixture was allowed to stand for 15 minutes at room temperature then diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass
1435 filter was transferred to a scintillation vial, and 5 mL scintillation fluid was added. The radioisotope retained on the glass fiber filter was counted to reflect the activity of the enzymes. The IC₅₀ value was calculated by measuring the activity of the enzyme over a suitable range of inhibitor concentrations.

Additionally, the ability of the compounds of the invention to inhibit prenylation in
1440 whole cells, inhibit anchorage-independent tumor cell growth and inhibit human tumor xenograft in mice could be demonstrated according to the methods described in PCT Patent Application No. WO95/25086, published September 21, 1995, which is hereby incorporated herein by reference.

1445 Pharmaceutical Compositions

The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. These salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate,
1450 cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate,

glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be
1455 quaternized with such agents as loweralkyl halides (such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides), dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-
1460 soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

1465 Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I)-(XII) or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Such pharmaceutically acceptable salts include, but are not limited to, cations based on the
1470 alkali and alkaline earth metals such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like as well as nontoxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like. Other representative organic amines useful for the formation of
1475 base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The compounds of the invention are useful (in humans and other mammals) for inhibiting protein isoprenyltransferases (i.e., protein farnesyltransferase and/or protein geranylgeranyltransferase) and the isoprenylation (i.e., farnesylation and/or
1480 geranylgeranylation) of Ras. These inhibitors of protein isoprenyltransferases are also useful for inhibiting or treating cancer in humans and other mammals. Examples of cancers which may be treated with the compounds of the invention include, but are not limited to, carcinomas such as lung, colorectal, bladder, breast, kidney, ovarian, liver, exocrine pancreatic, cervical, esophageal, stomach and small intestinal; sarcomas such as oesteroma,
1485 osteosarcoma, lepoma, liposarcoma, hemanioma and hemangiosarcoma; melanomas such as amelanotic and melanotic; mixed types of cancers such as carcinosarcoma, lymphoid tissue type, follicular reticulum, cell sarcoma and Hodgkins disease and leukemias, such as

myeloid, acute lymphoblastic, chronic lymphocytic, acute myeloblastic and chronic myelocytic.

1490 The ability of the compounds of the invention to inhibit or treat cancer can be demonstrated according to the methods of Mazerska Z., Woynarowska B., Stefanska B., Borowski S., *Drugs Exptl. Clin. Res.* 13(6), 345-351 (1987) Bissery, M.C., Guenard F., Guerritte-Voegelein F., Lavelle F., *Cancer Res.* 51, 4845-4852 (1991) and Rygaard J., and Povlsen C., *Acta Pathol. Microbiol. Scand.* 77, 758 (1969), which are hereby incorporated
1495 herein by reference.

 These inhibitors of protein isoprenyltransferases are also useful for treating or preventing restenosis in humans and other mammals. The ability of the compounds of the invention to treat or prevent restenosis can be demonstrated according to the methods described by Kranzhofer, R. et al. *Circ. Res.* 73: 264-268 (1993), Mitsuka, M. et al.
1500 *Circ. Res.* 73: 269-275 (1993) and Santoian, E.C. et al. *Circulation* 88: 11-14 (1993), which are hereby incorporated herein by reference.

 For use as a chemotherapeutic agent, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.01 to 500 mg/kg body weight daily, preferably in amounts from 0.1 to 20 mg/kg body weight daily and more
1505 preferably in amounts from 0.5 to 10 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

 For treatment or prevention of restenosis, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 50 mg/kg body weight daily. Dosage unit
1510 compositions may contain such amounts of submultiples thereof to make up the daily dose.

 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

 It will be understood, however, that the specific dose level for any particular patient
1515 will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

 The compounds of the present invention may be administered orally, parenterally,
1520 sublingually, by inhalation spray, rectally or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes

subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Injectable preparations, for example sterile injectable aqueous or oleagenous suspensions, may be formulated according to the known art using suitable dispersing or wetting and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent (as in a solution in 1,3-propanediol, for example). Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Additionally, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. These dosage forms may also comprise additional substances other than inert diluents such as lubricating agents like magnesium stearate. With capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills may also be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water. Such compositions may also comprise adjuvants such as wetting agents, emulsifying and suspending agents and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*, which is hereby incorporated herein by reference.

While the compounds of the invention can be administered as the sole active pharmaceutical agent for the treatment of cancer, they can also be used in combination with one or more other chemotherapeutic agents.

Representative examples of chemotherapeutic agents are described in Holleb, et al.,
1565 Clinical Oncology, American Cancer Society, United States (1991) p 56 *et seq.*, which is hereby incorporated herein by reference. These agents include alkylating agents such as the nitrogen mustards (mechloethamine, melphalan, chlorambucil, cyclophosphamide and ifosfamide), nitrosoureas (carmustine, lomustine, semustine, streptozocin), alkyl sulfonates (busulfan), triazines (dacarbazine) and ethylenimines (thiotepa, hexamethylmelamine); folic
1570 acid analogues (methotrexate); pyrimidine analogues (5-fluorouracil, cytosine arabinoside); purine analogues (6-mercaptopurine, 6-thioguanine); antitumor antibiotics (actinomycin D, the anthracyclines (doxorubicin), bleomycin, mitomycin C, methramycin); plant alkaloids such as vinca alkaloids (vincristine and vinblastine) and etoposide (VP-16); hormones and hormone antagonists (tamoxifen and corticosteroids); and miscellaneous agents (cisplatin,
1575 taxol and brequinar).

The above compounds to be employed in combination with the isoprenyl protein transferase inhibitor of the invention will be used in therapeutic amounts as indicated in the Physicians' Desk Reference (PDR) 47th Edition (1993), which is incorporated herein by
1580 reference or by such therapeutically useful amounts as would be known to one of ordinary skill in the art.

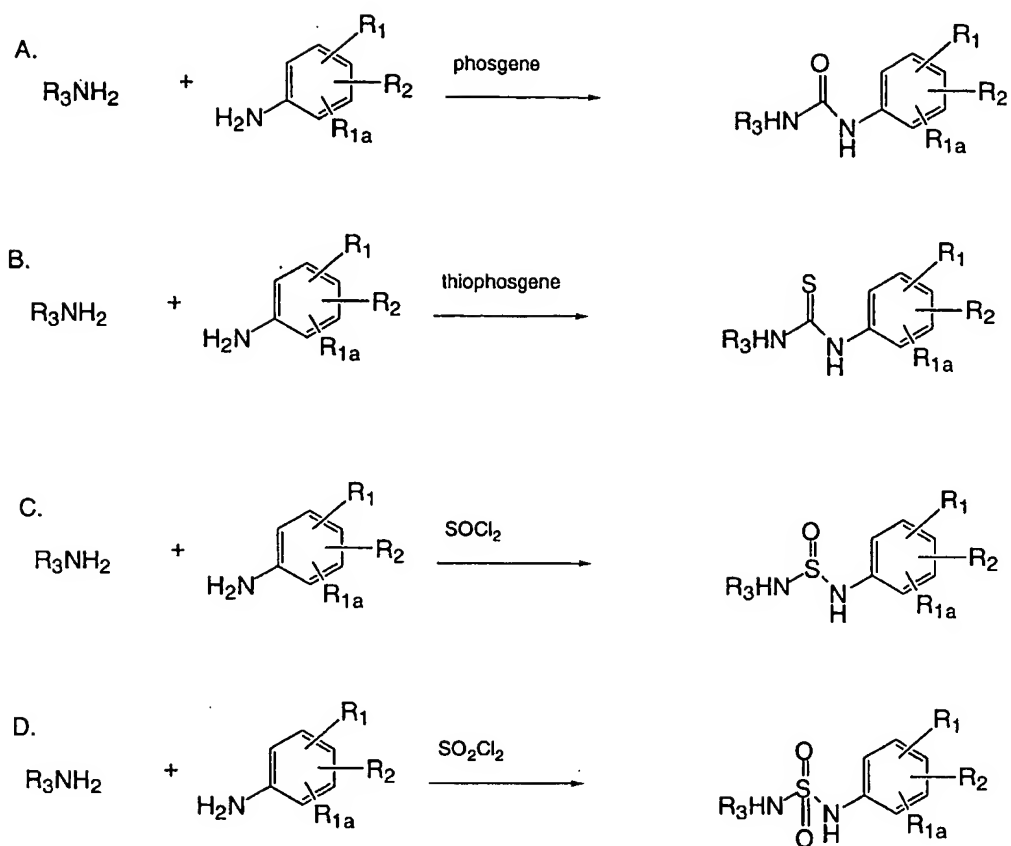
The compounds of the invention and the other chemotherapeutic agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied to obtain
1585 a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient.

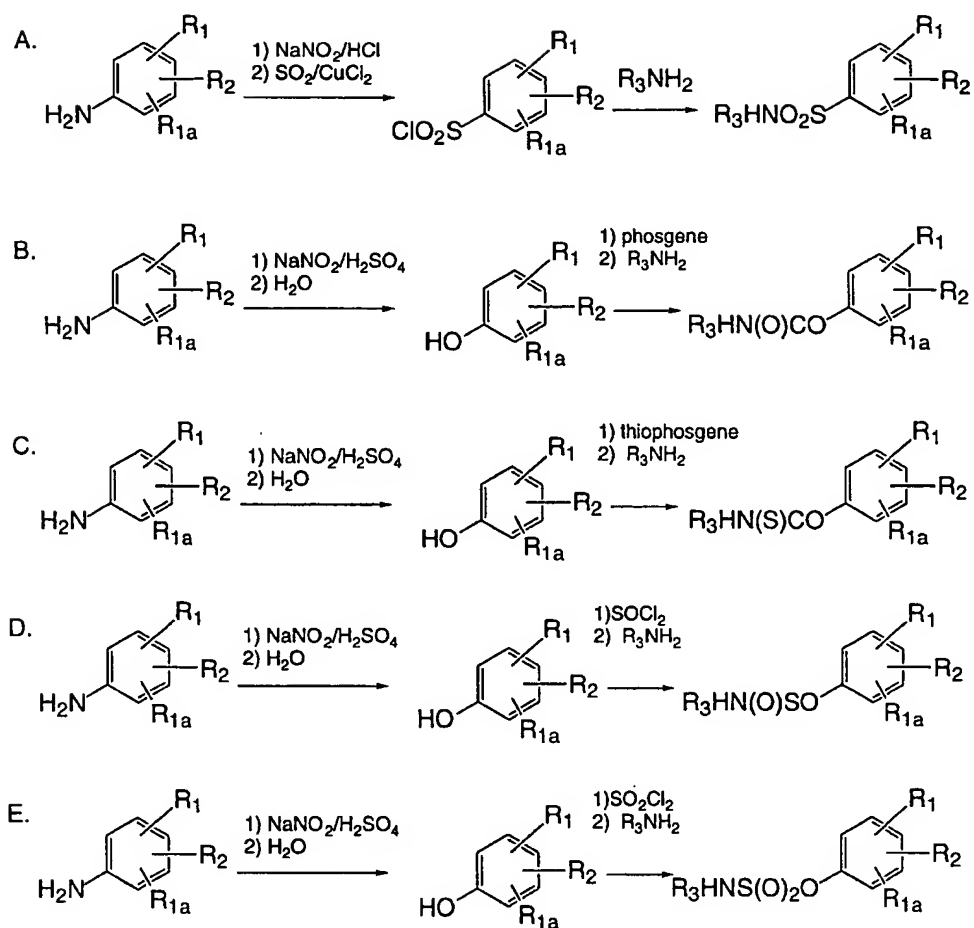
When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

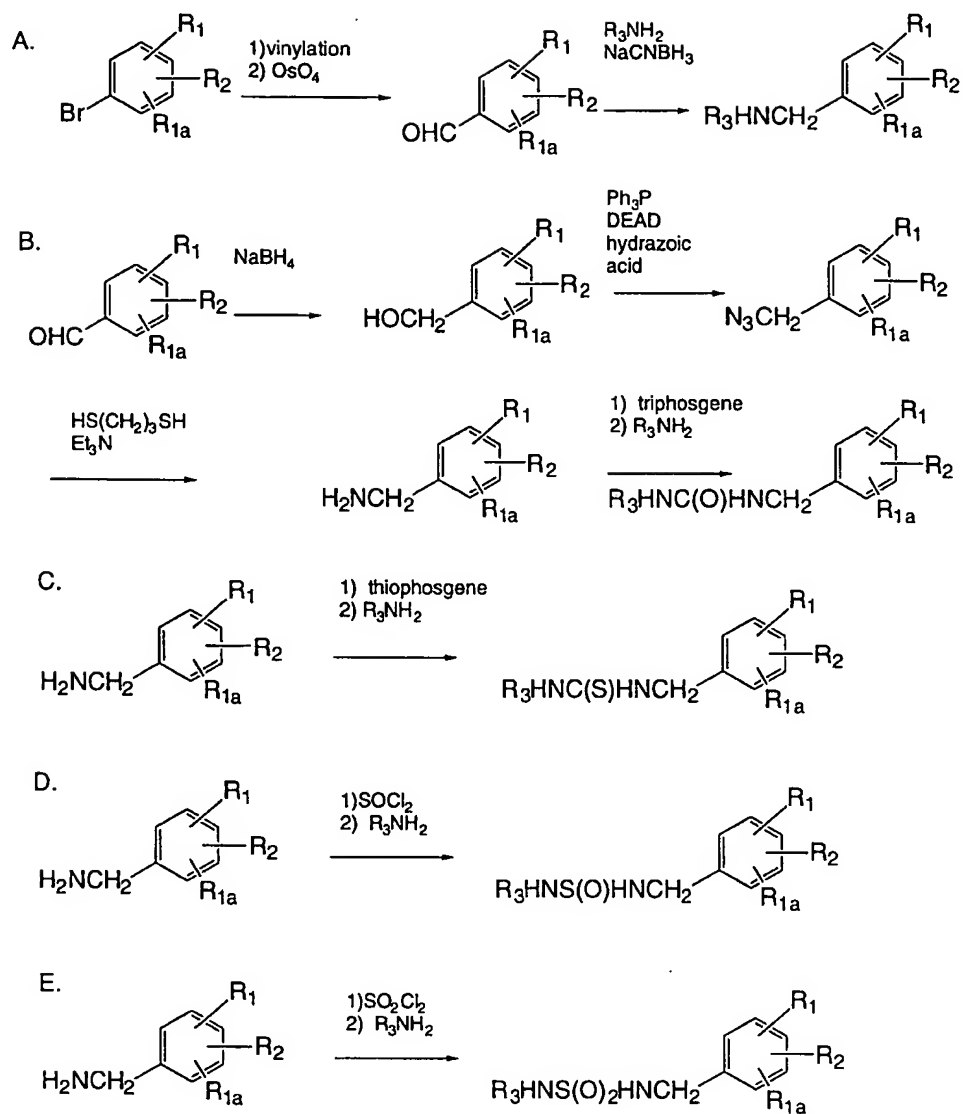
1590 Preparation of the Compounds of the Invention

In general, the compounds of the invention can be prepared by the processes illustrated in the following Schemes 1-16. In these general schemes compounds of the formula I are used to exemplify the methods, but the methods are intended to be applicable to all of the compounds of the invention.

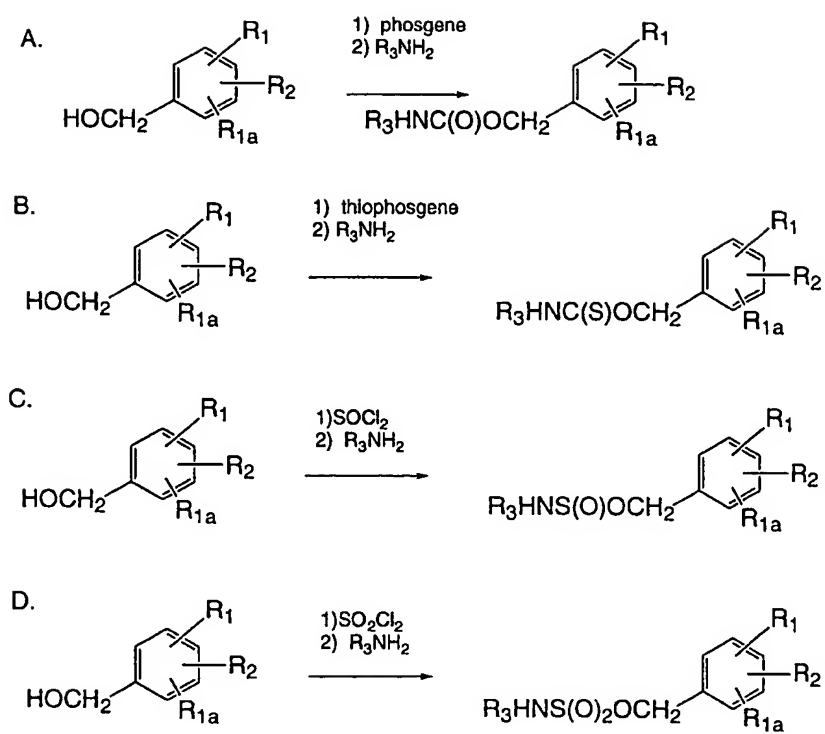
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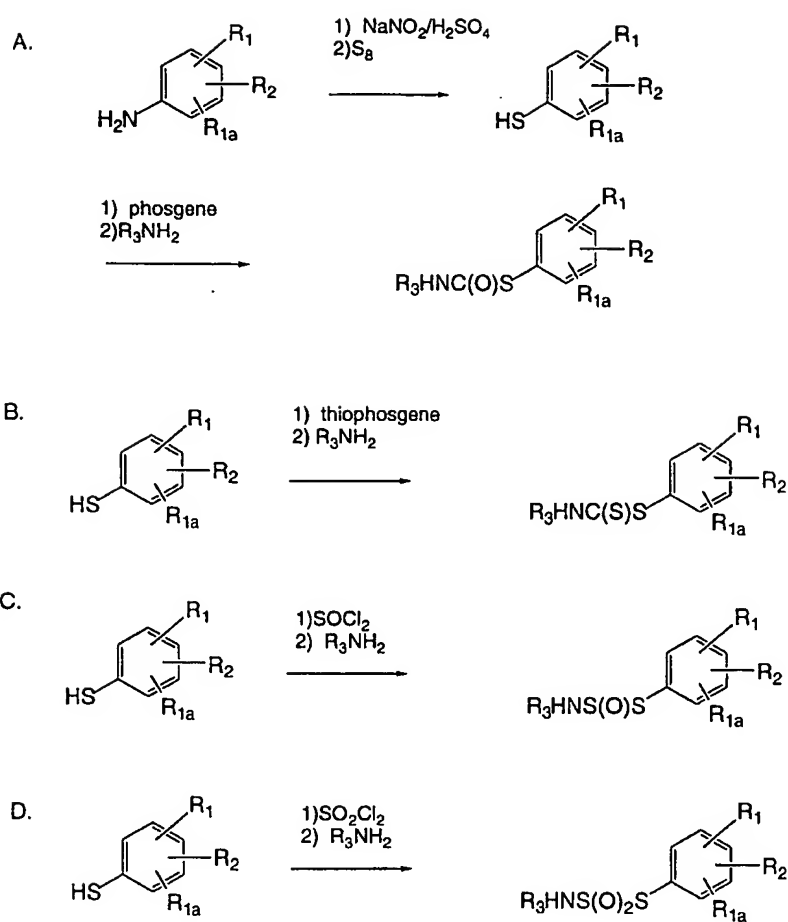
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SCHEME 2

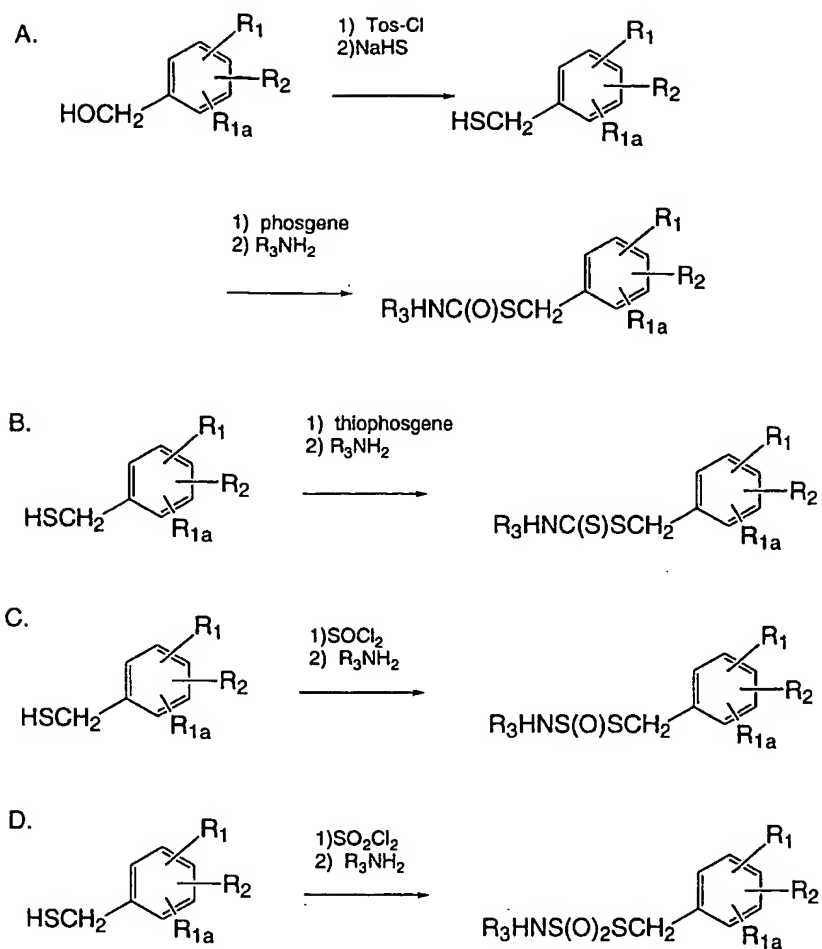
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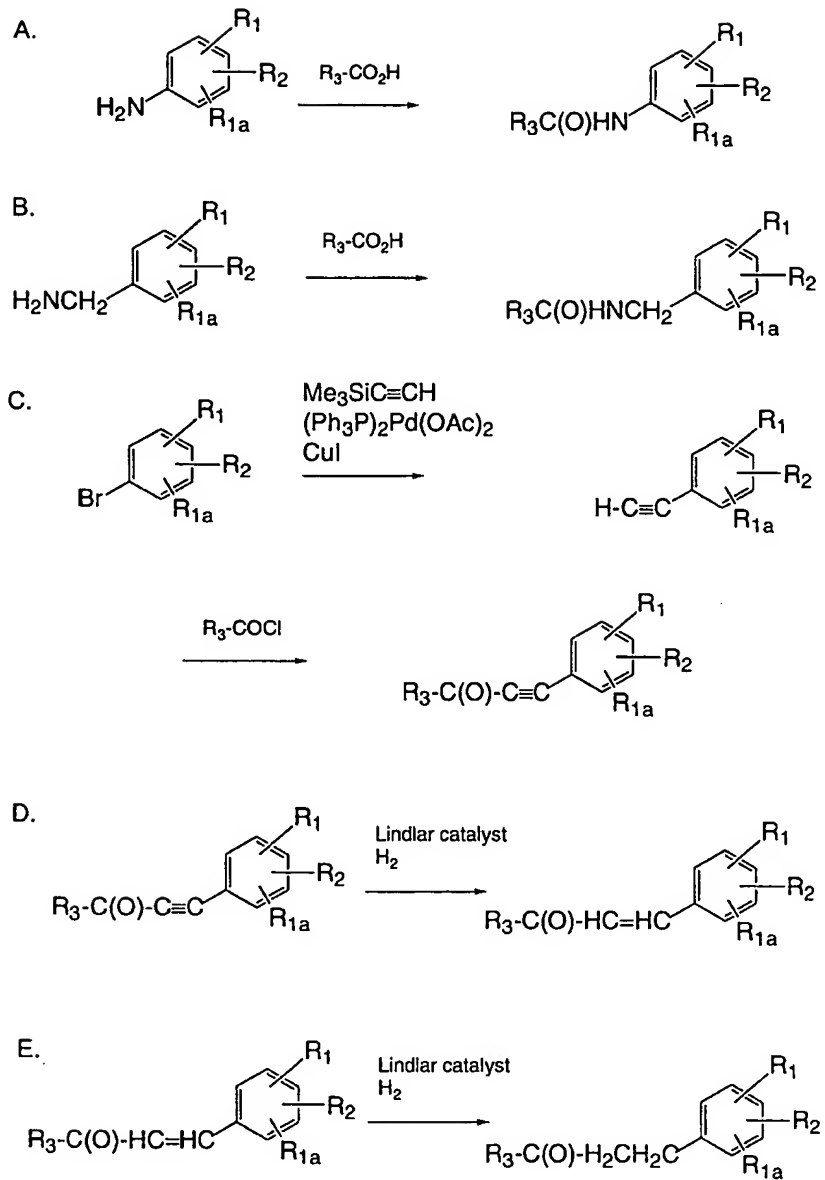
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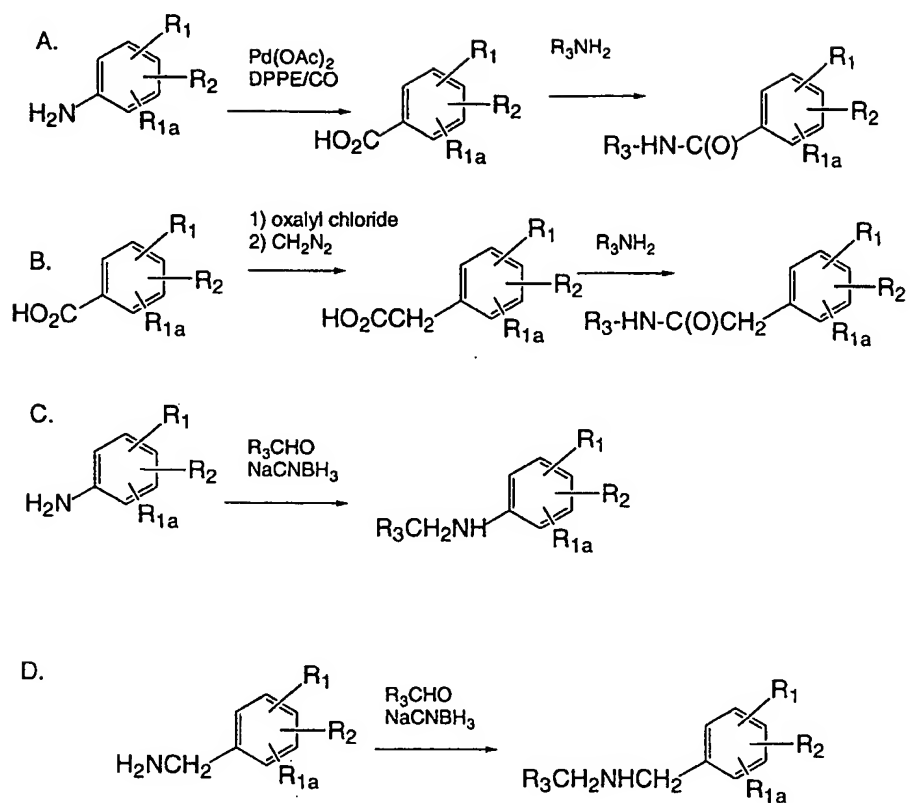
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SCHEME 5

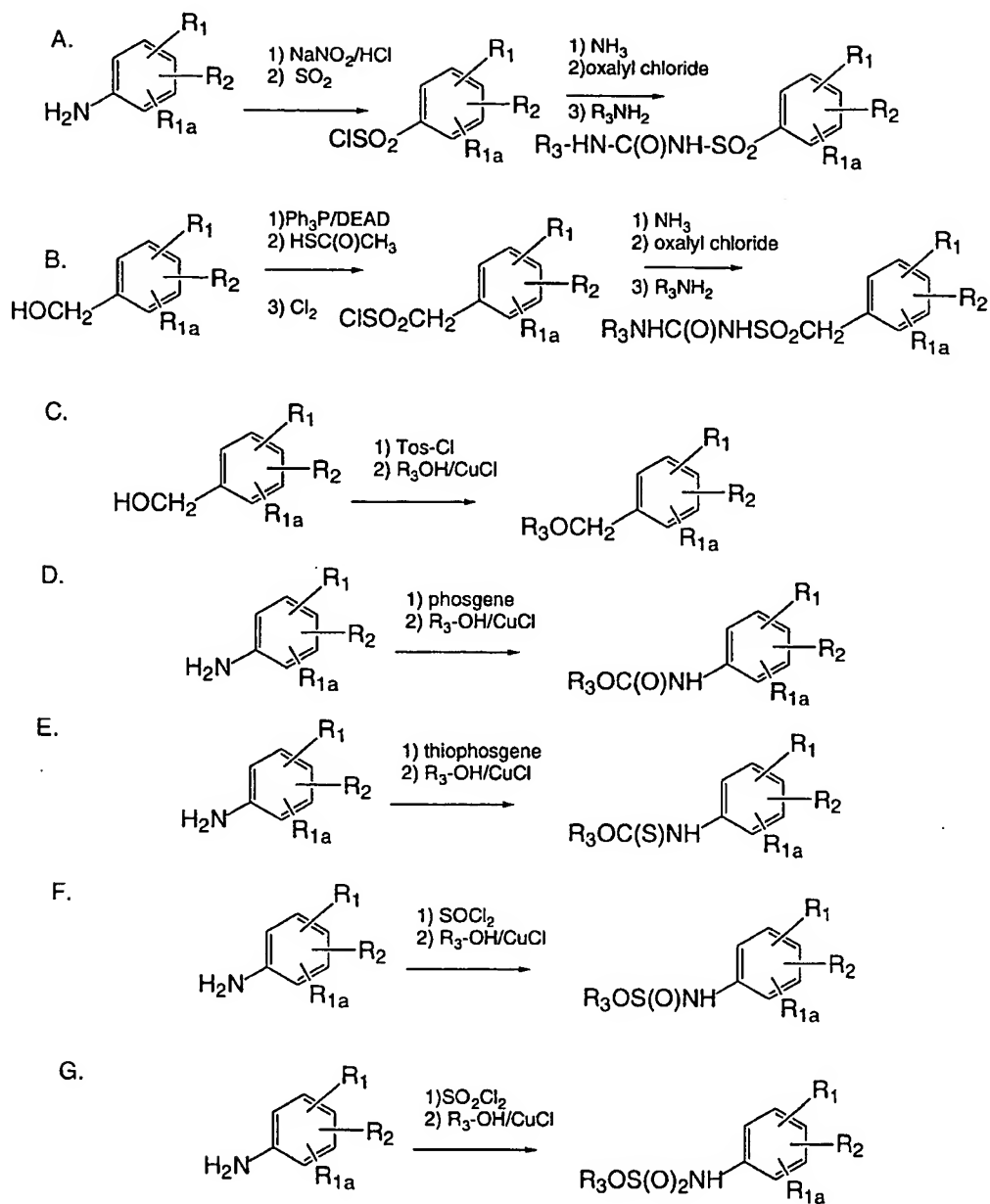
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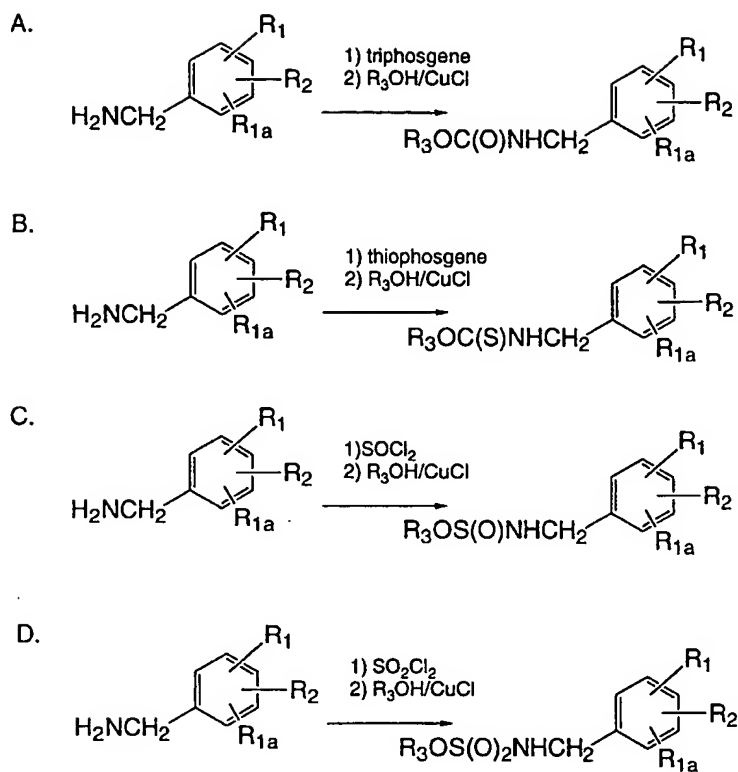
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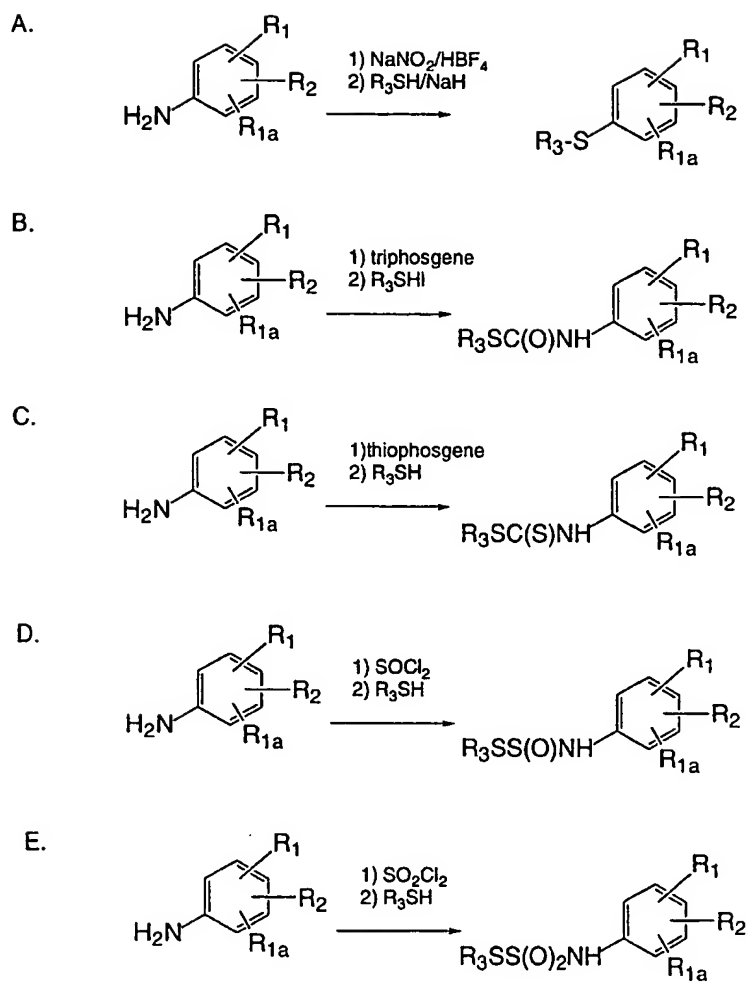
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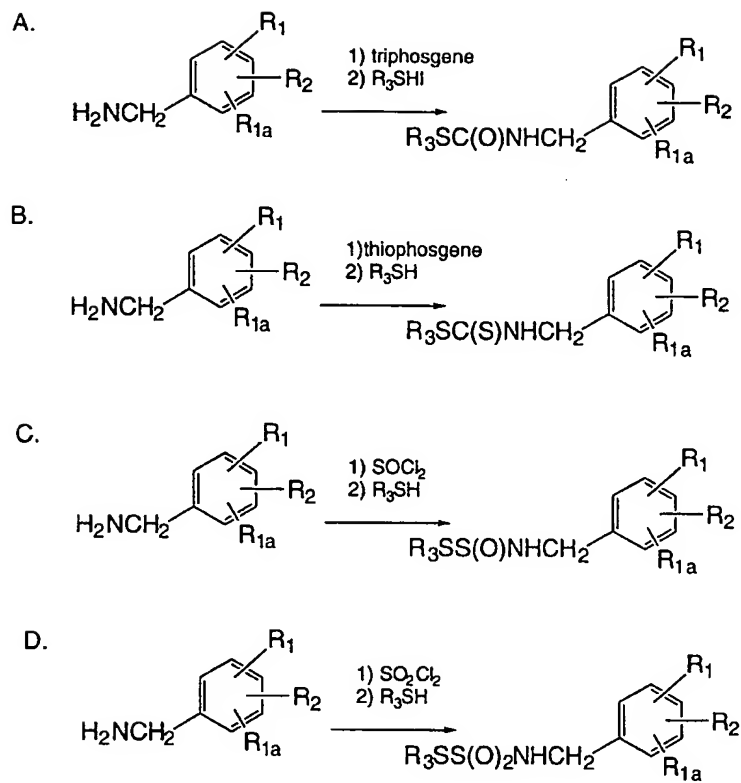
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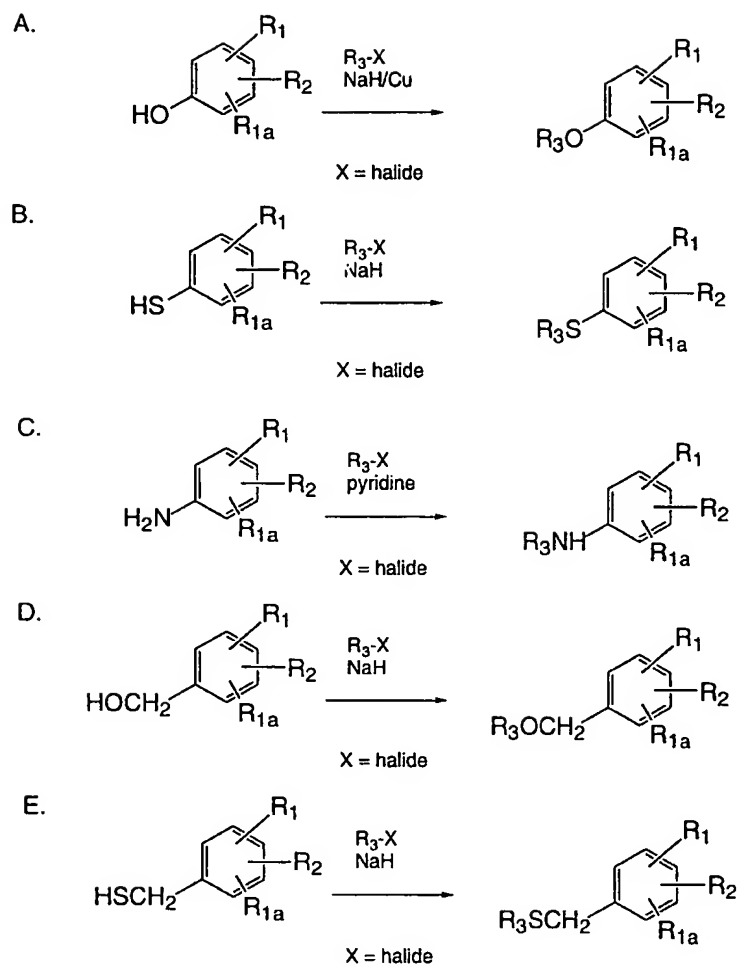
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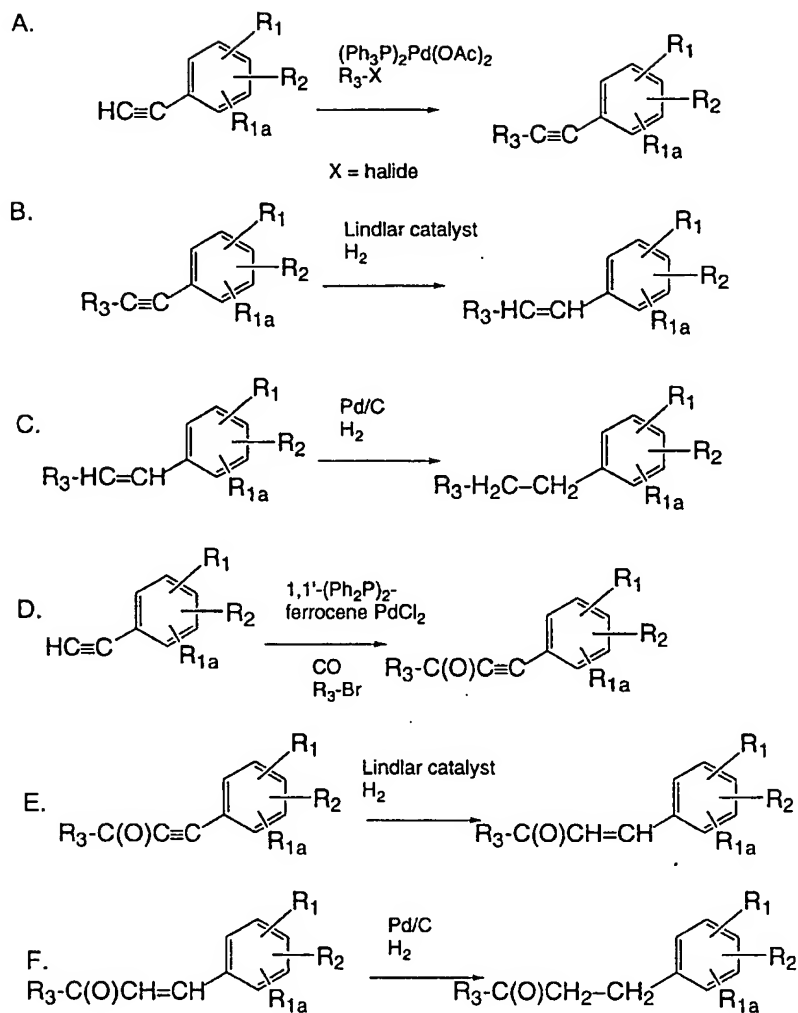
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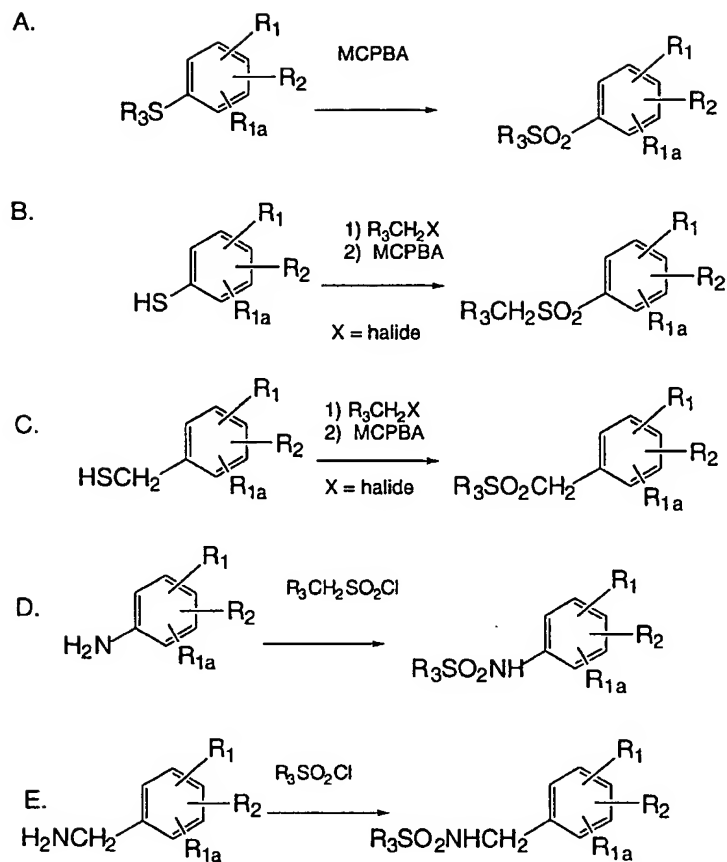
SCHEME 10

SCHEME 11

SCHEME 12

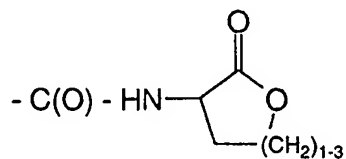
SCHEME 13

SCHEME 14

SCHEME 15

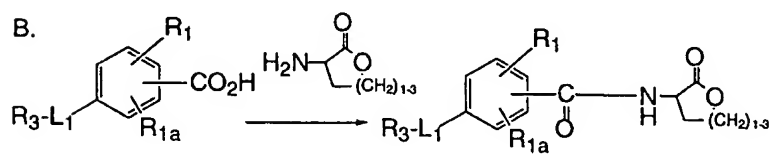
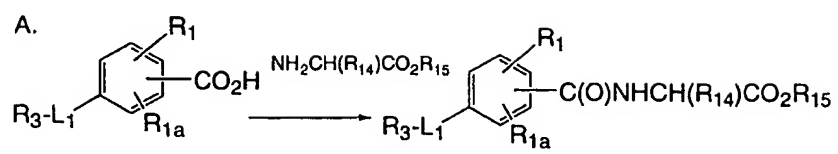
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Scheme 16 illustrates an alternative method for preparing compounds wherein R_2 is $-C(O)NH-CH(R_{14})-C(O)OR_{15}$ or

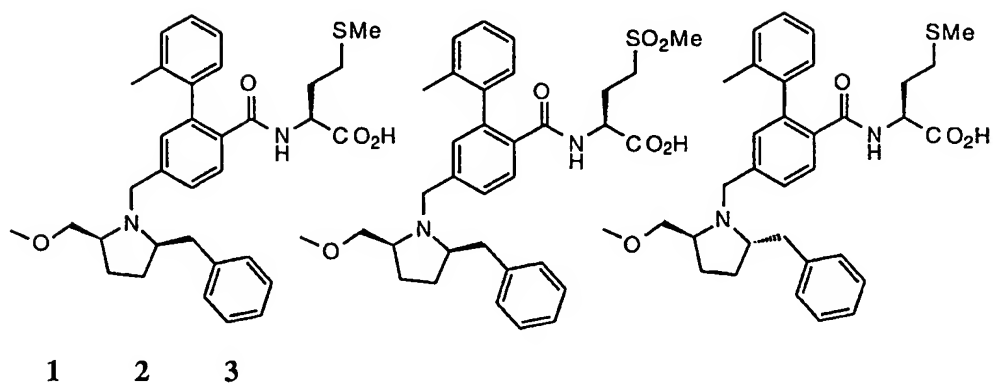


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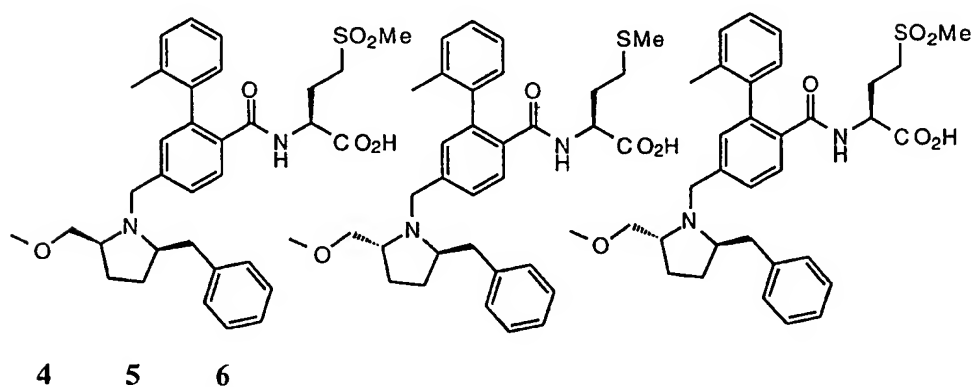
as defined above.

SCHEME 16

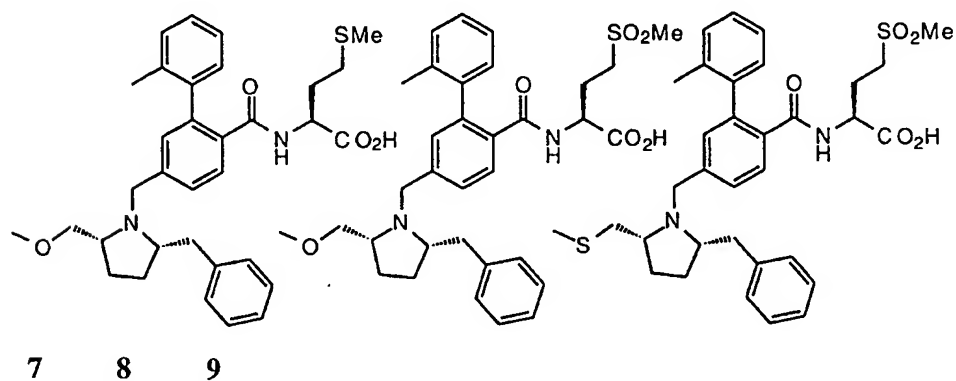
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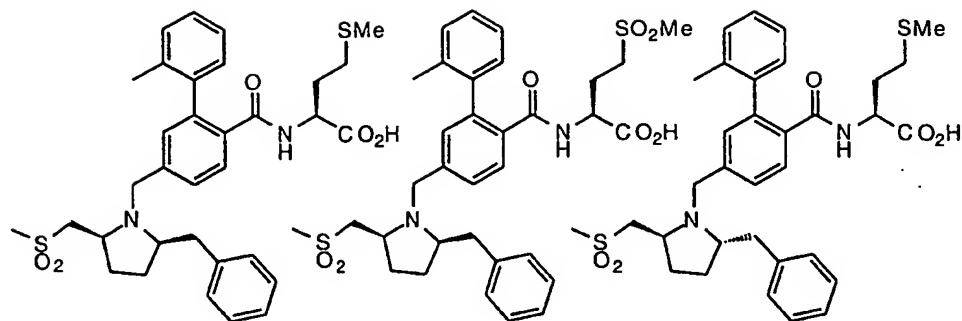
Table 6. Amines of the Type A(B)N-L₁

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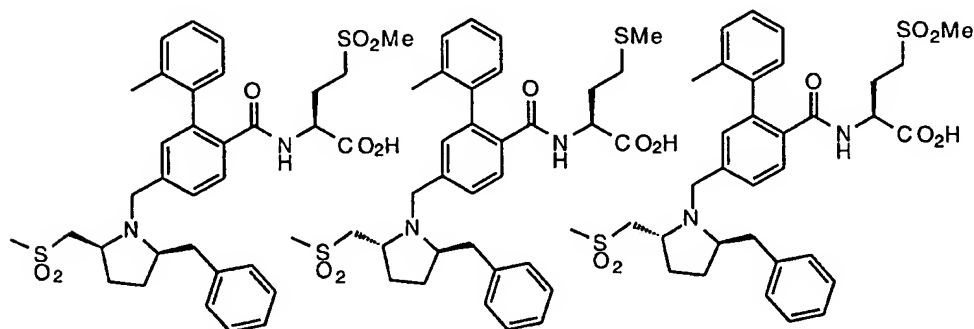


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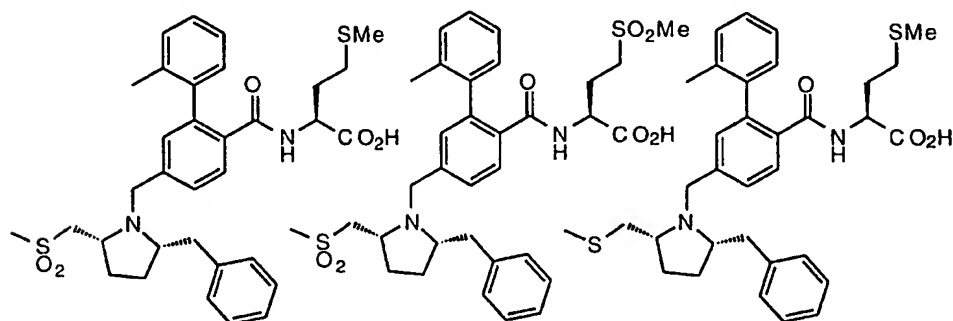


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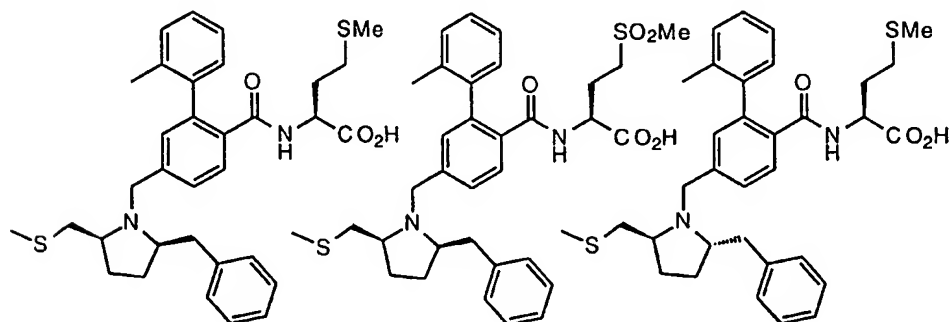


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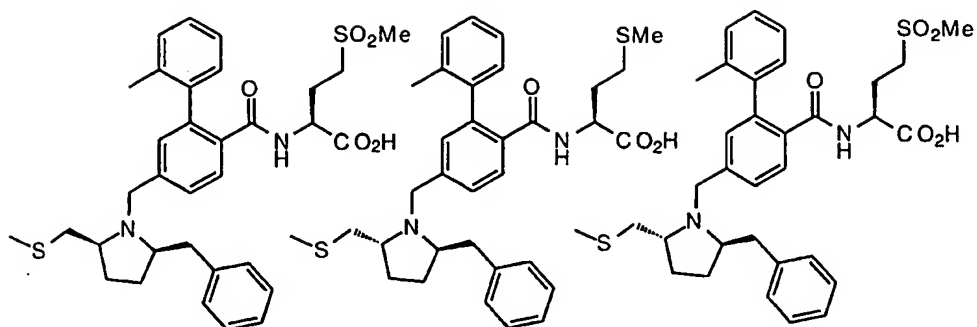


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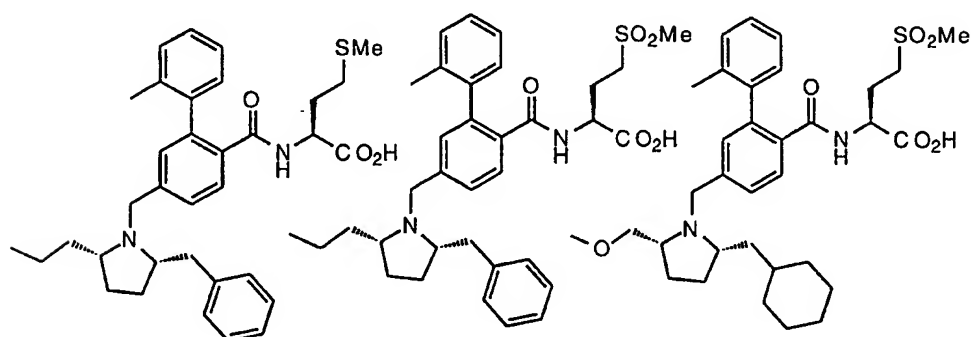


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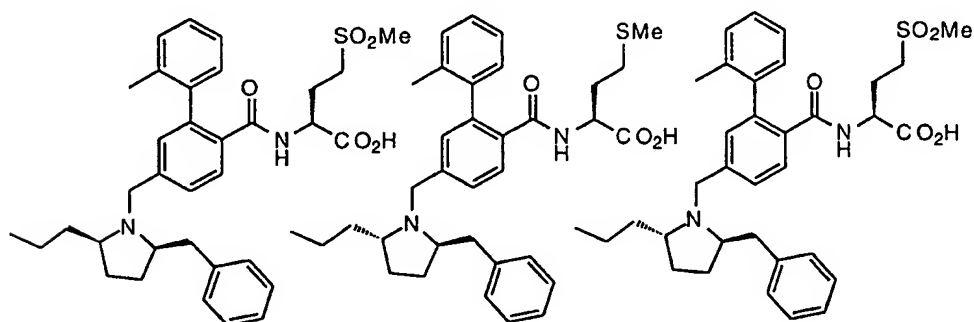
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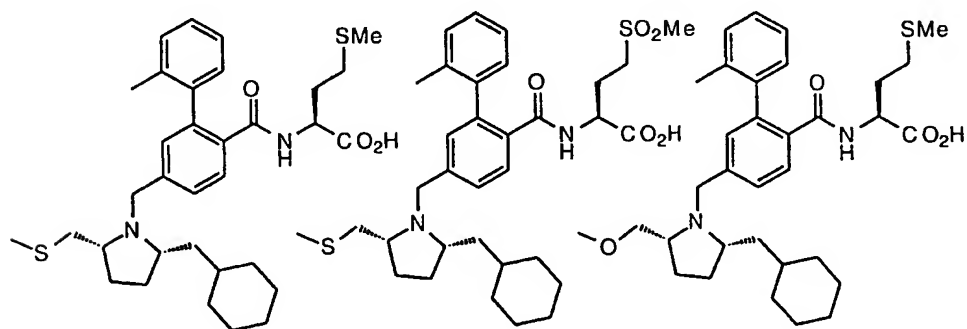
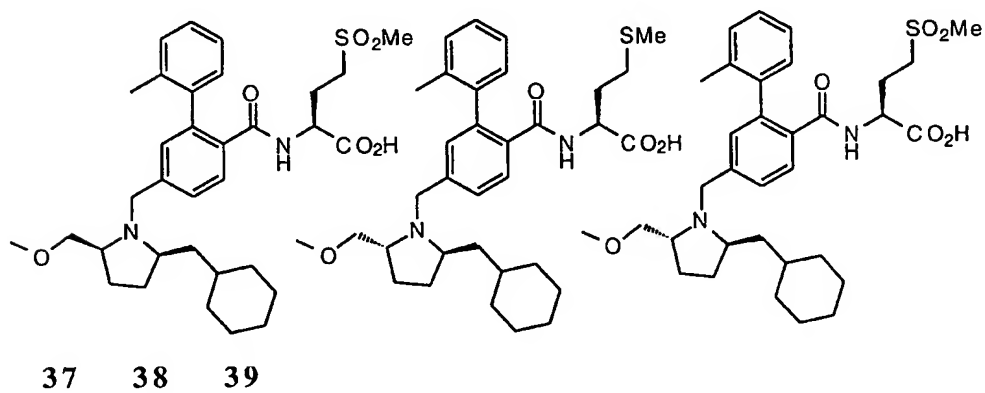
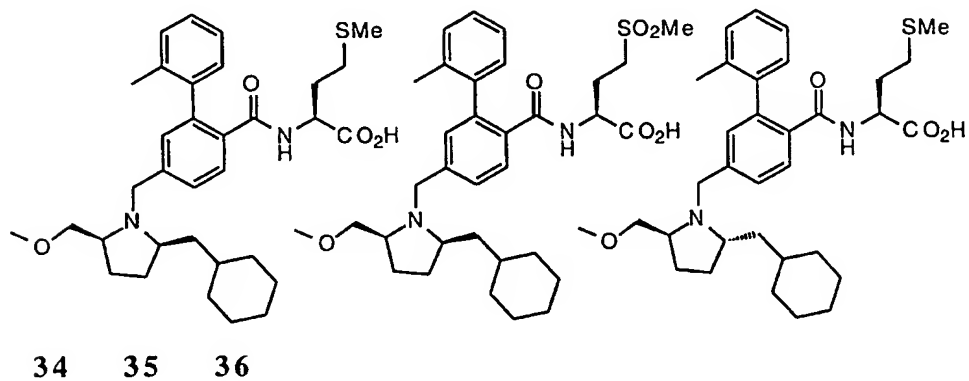
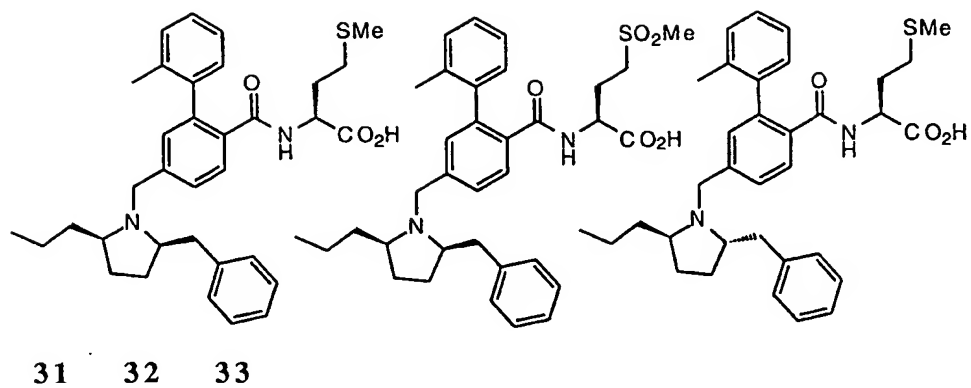
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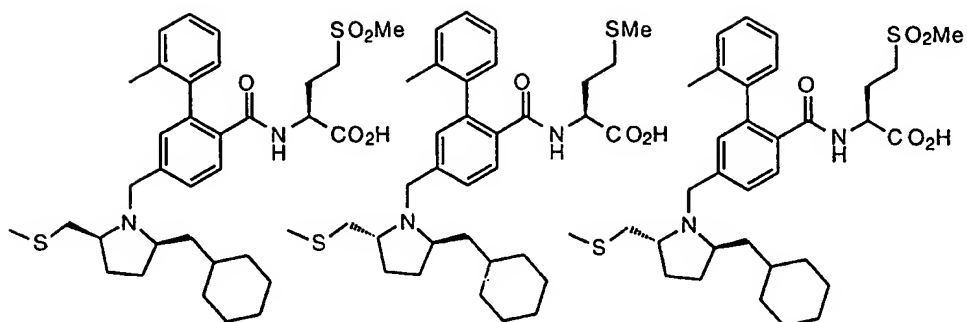
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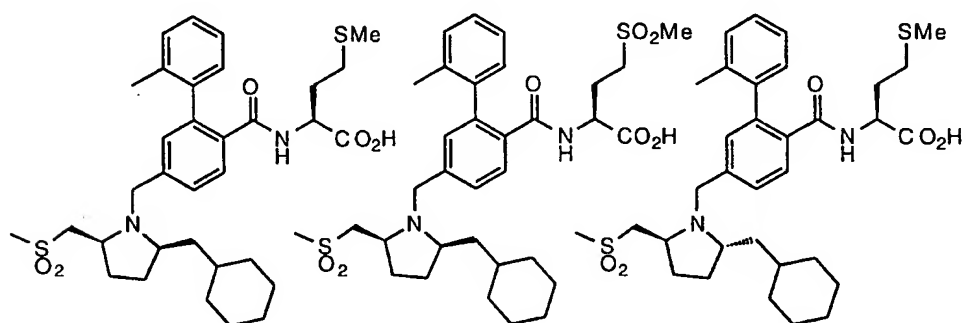


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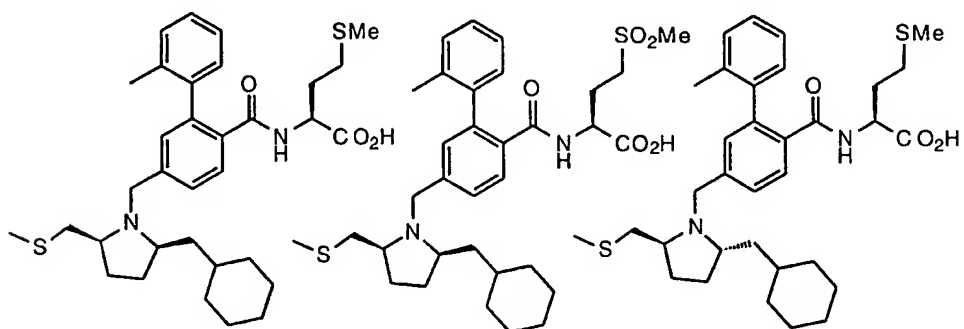


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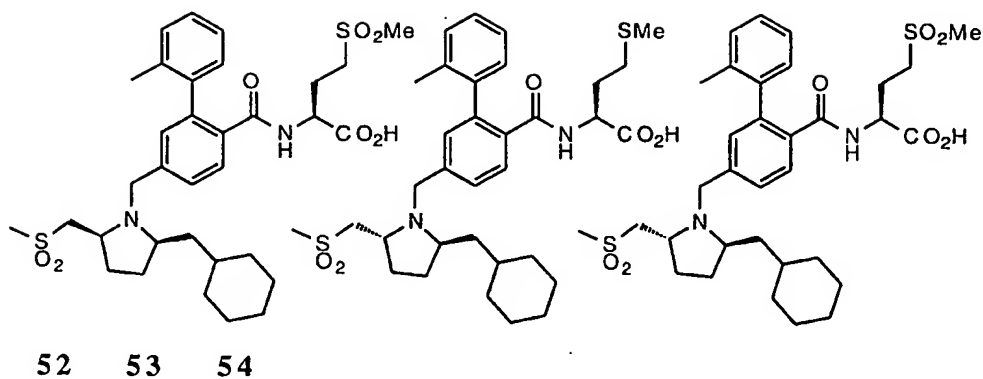
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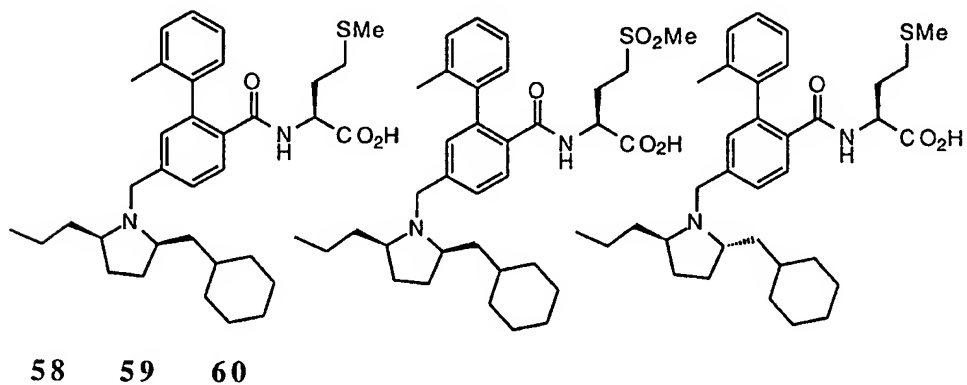
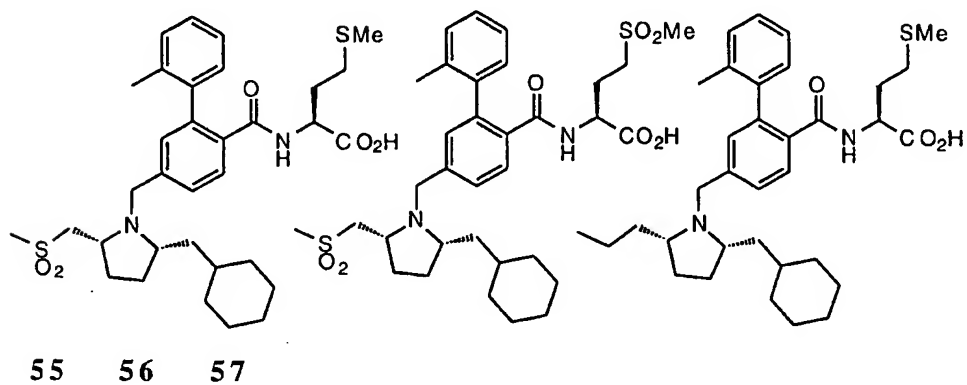
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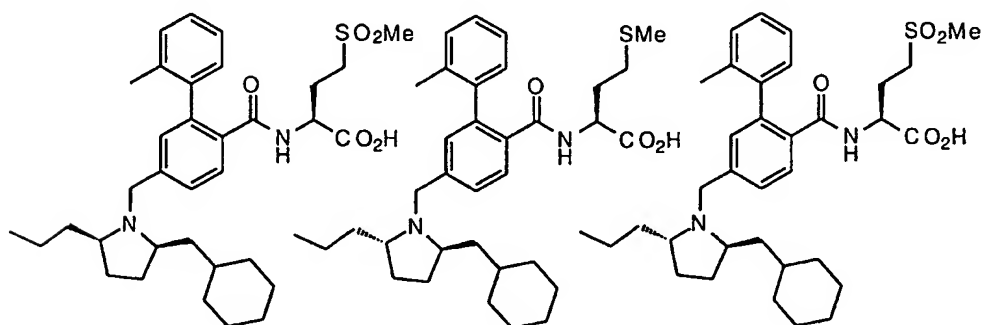




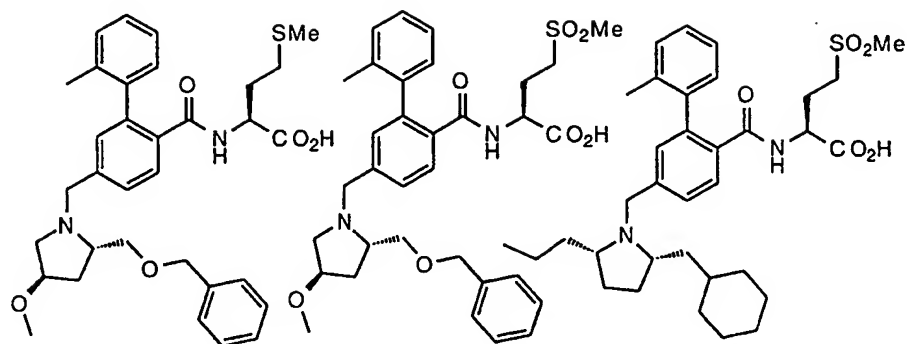
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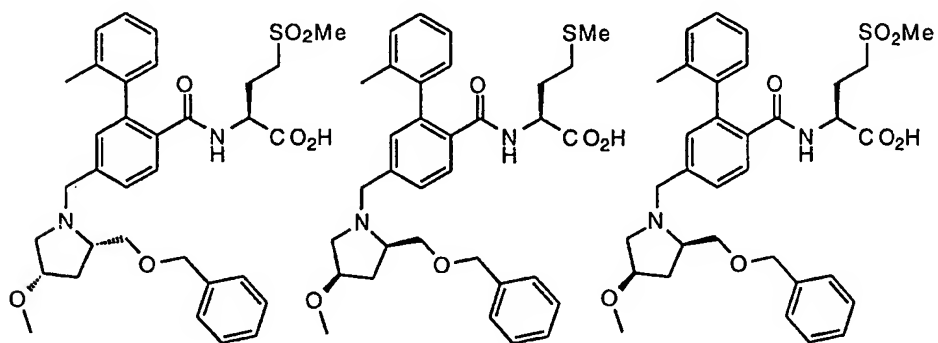


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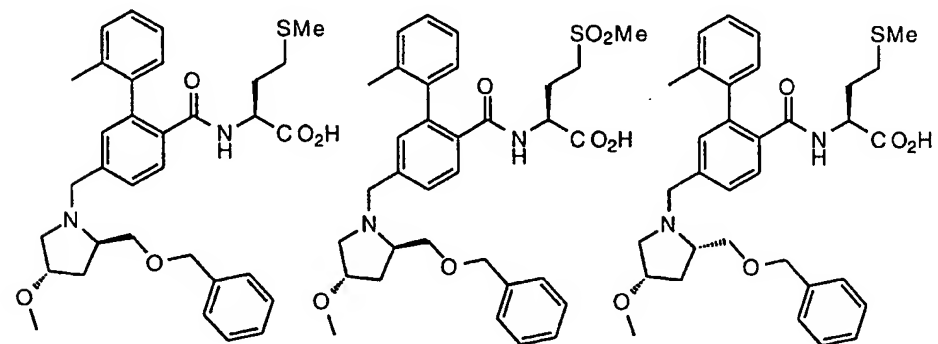


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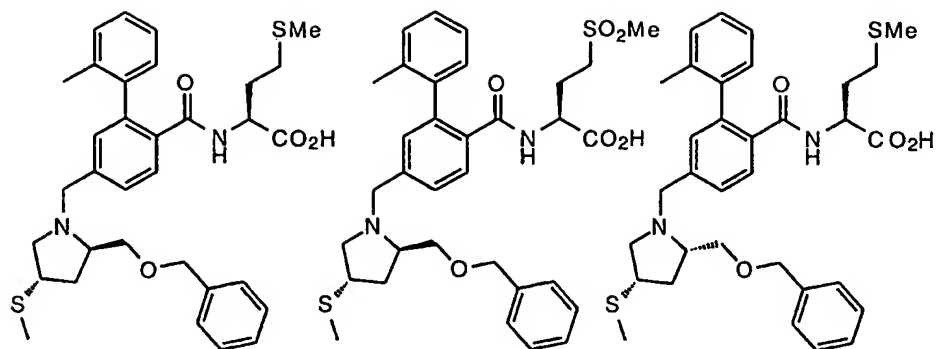
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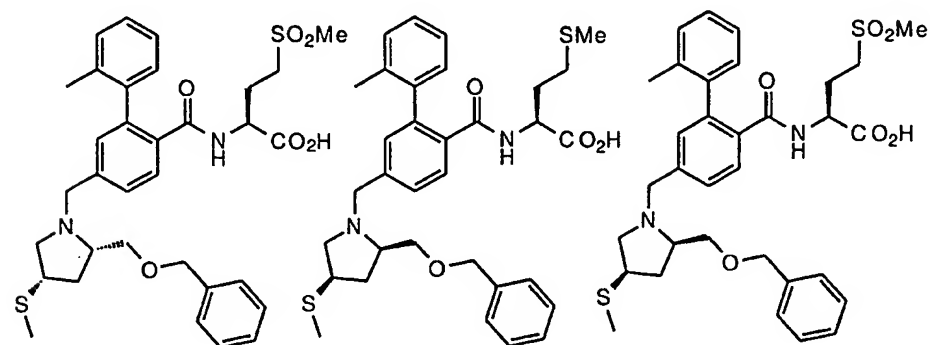


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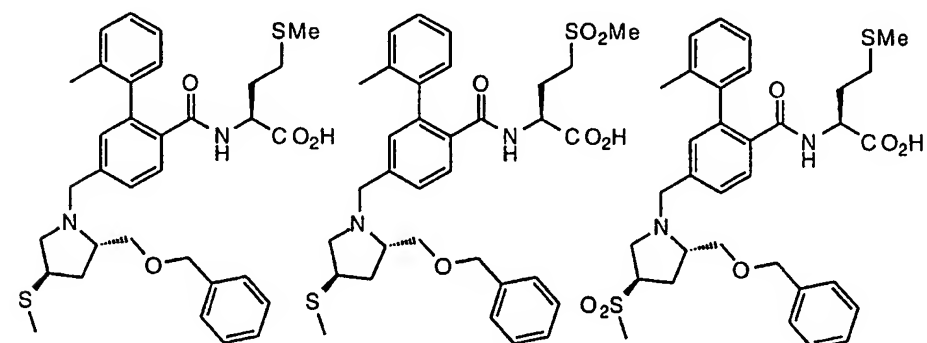


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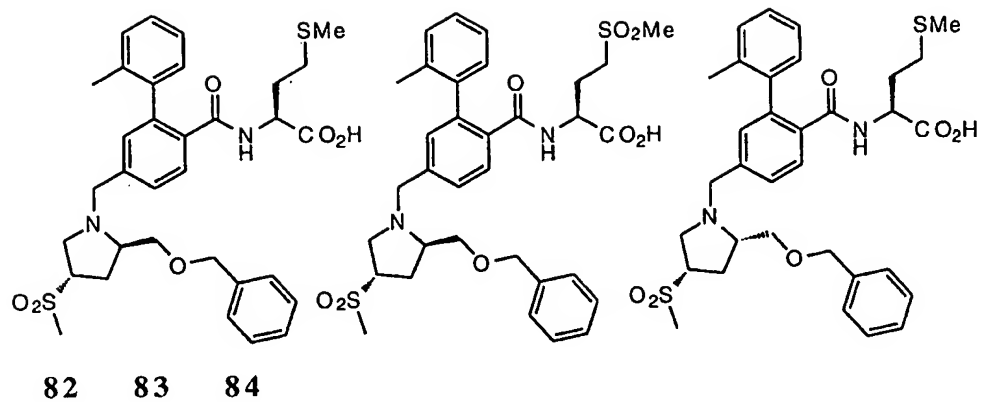


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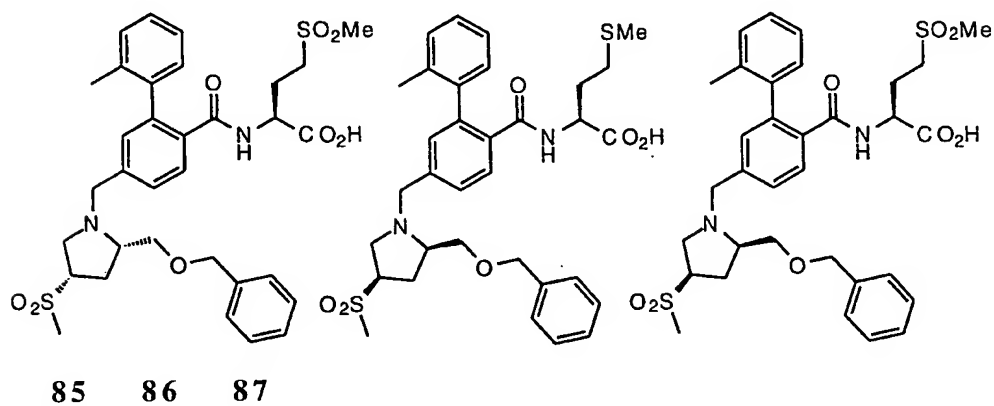


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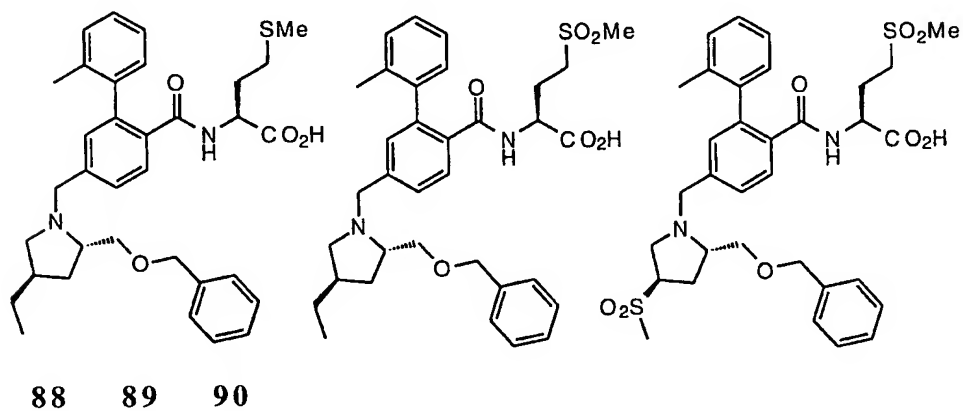
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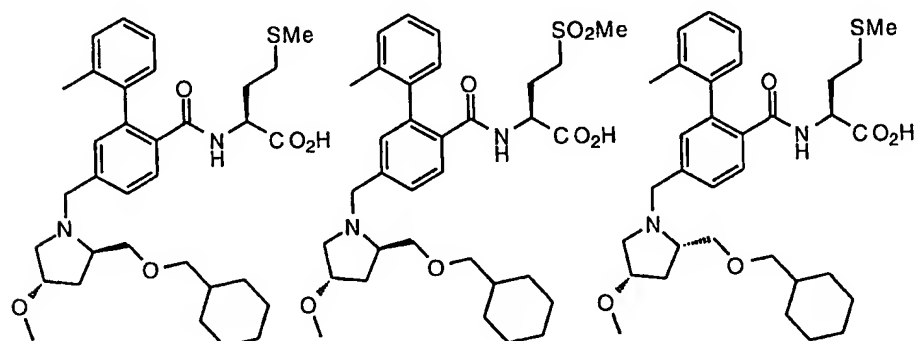
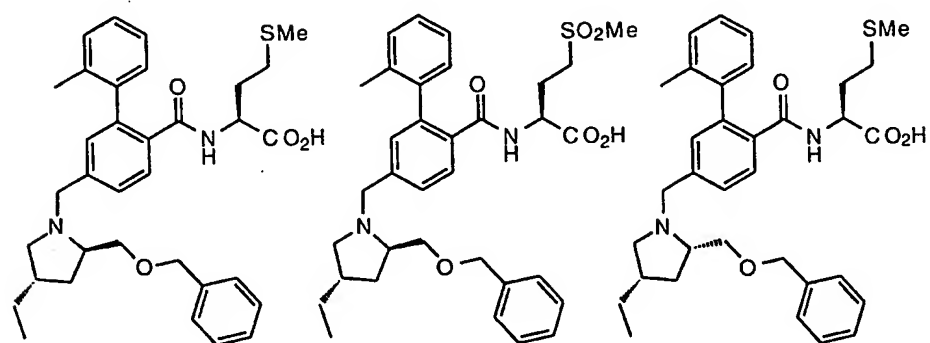
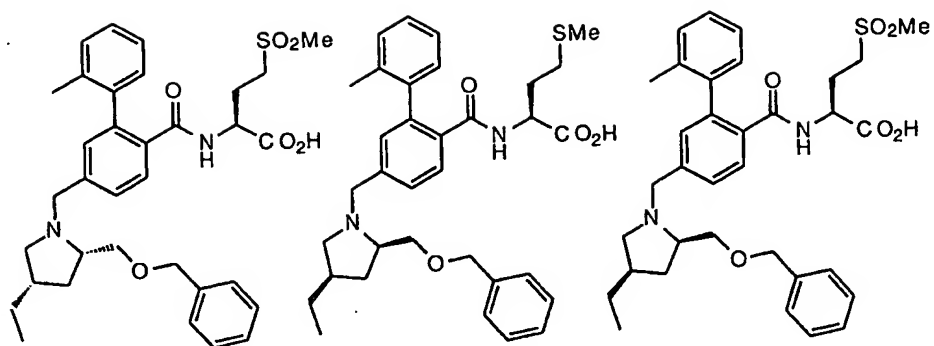


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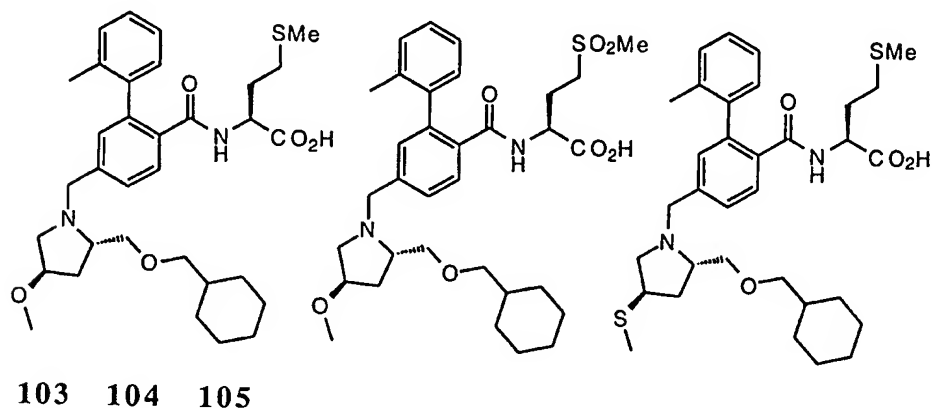
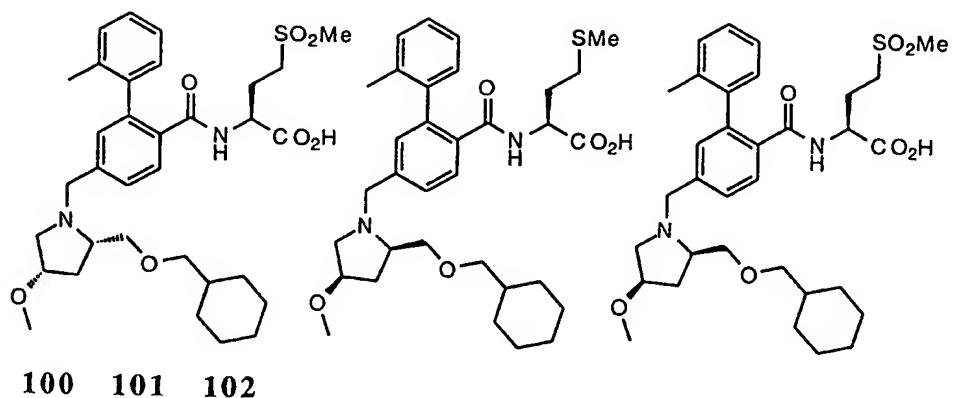
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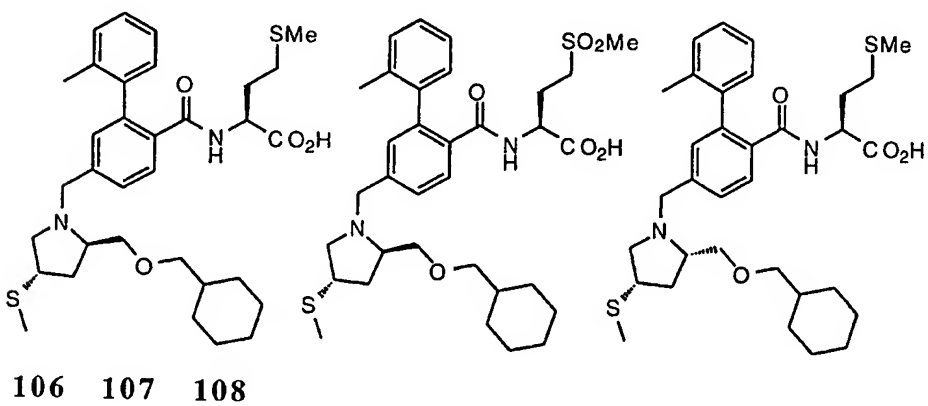


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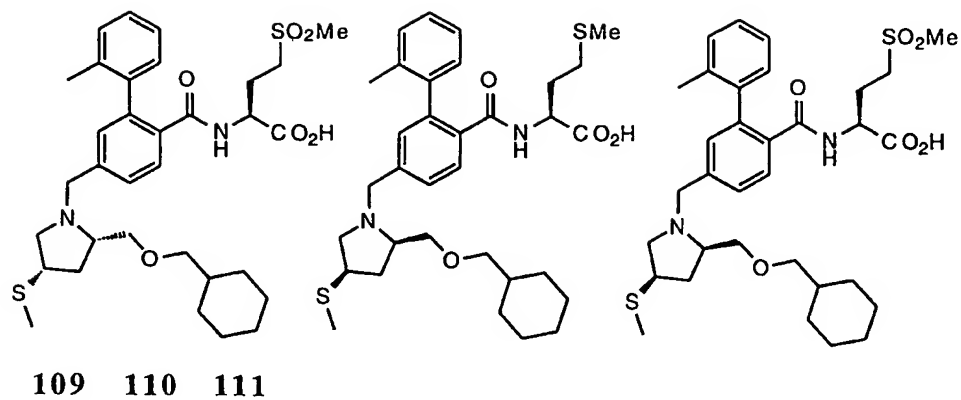
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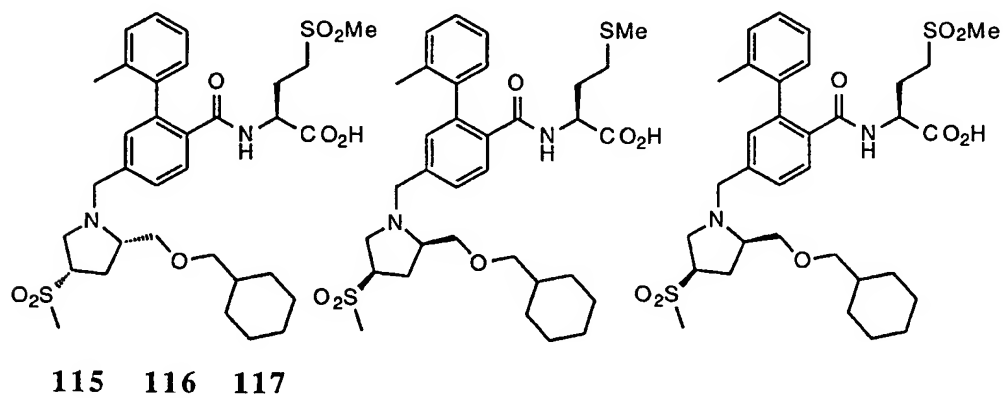
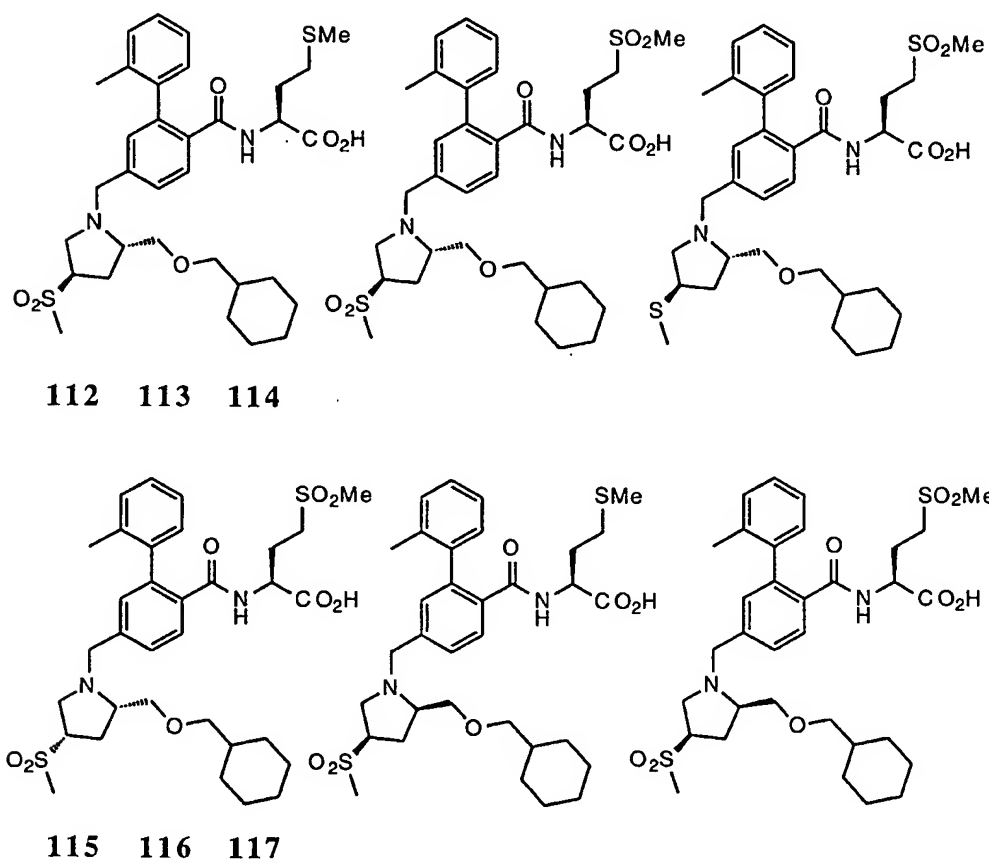
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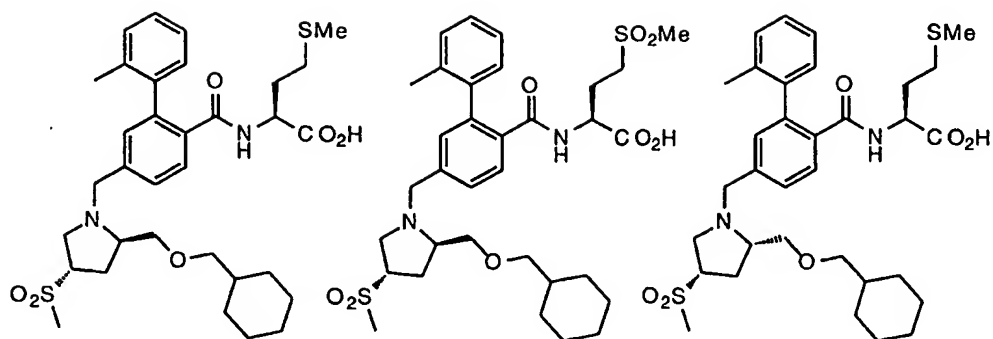


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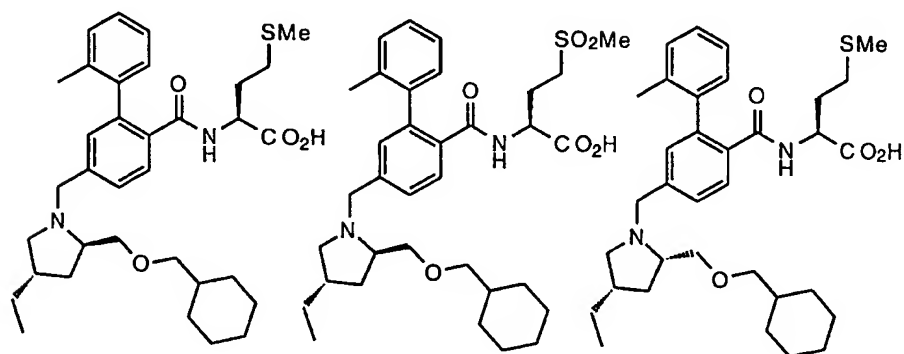
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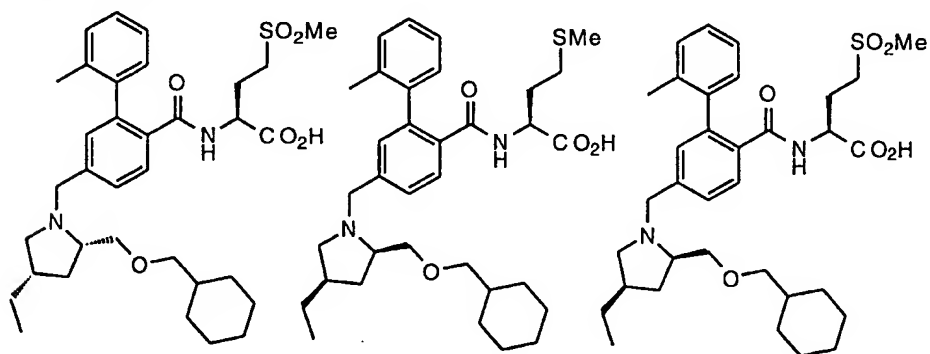


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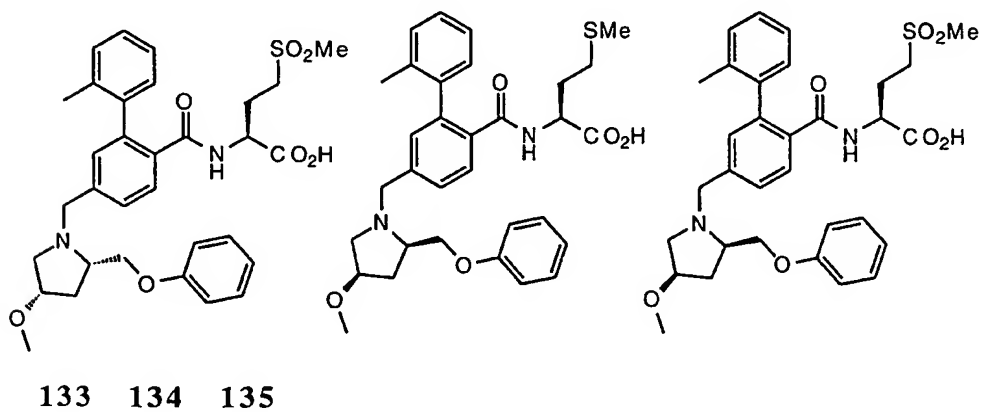
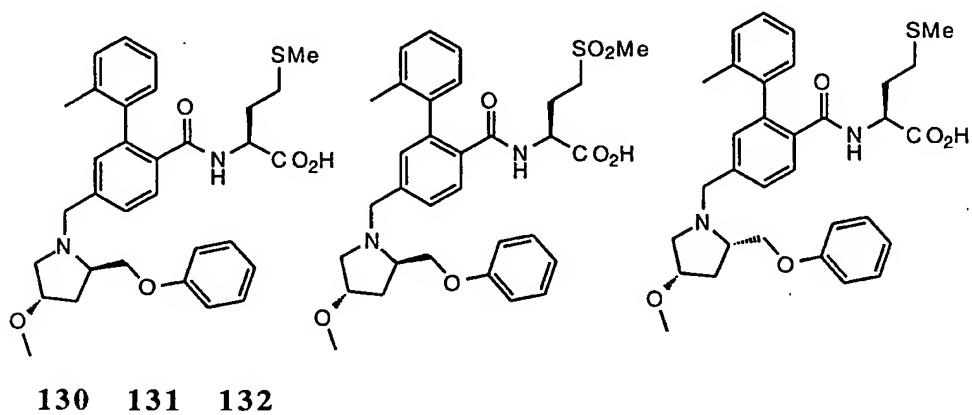
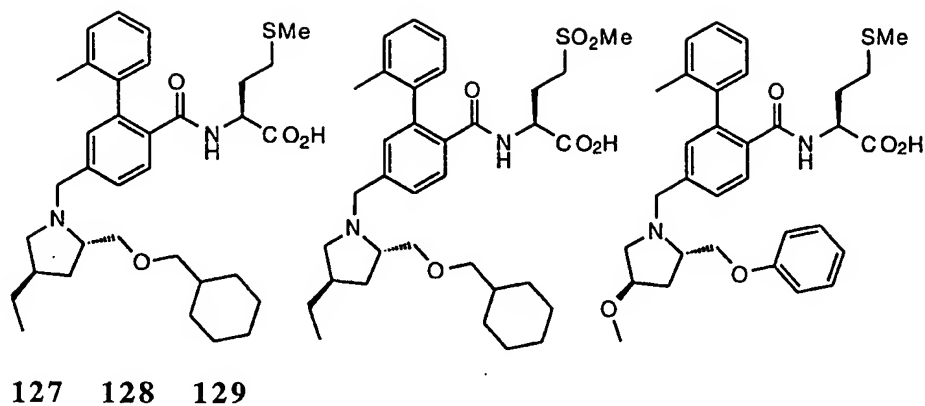


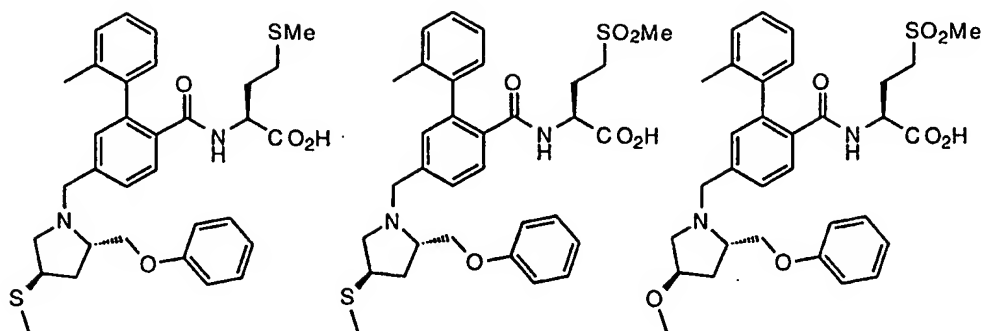
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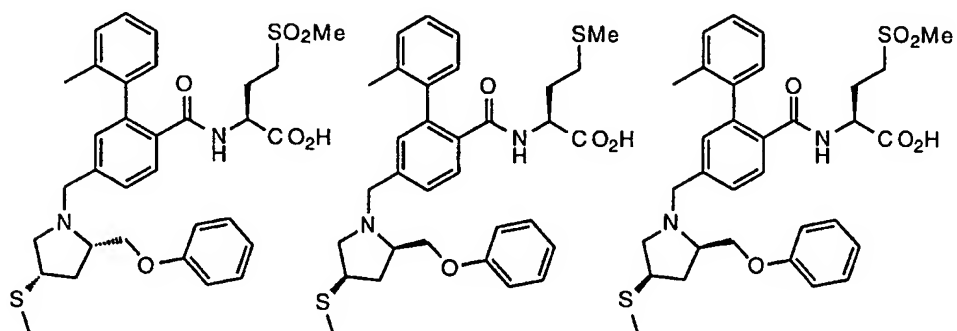
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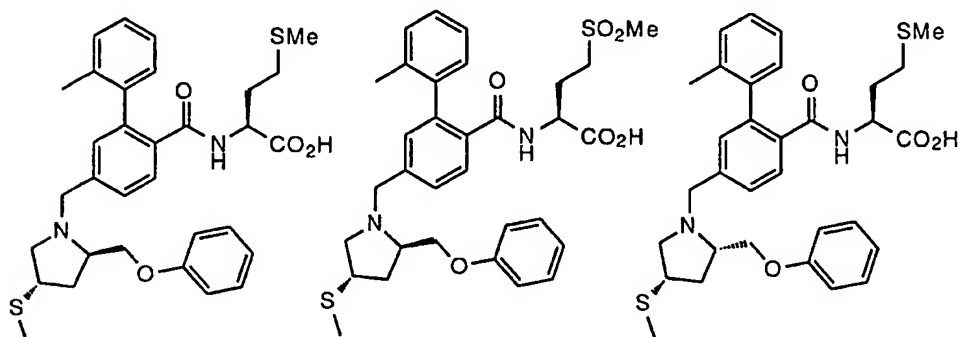


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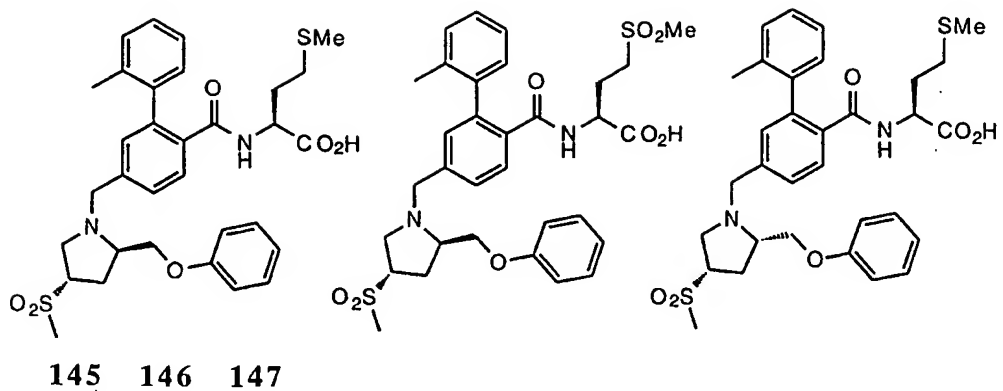
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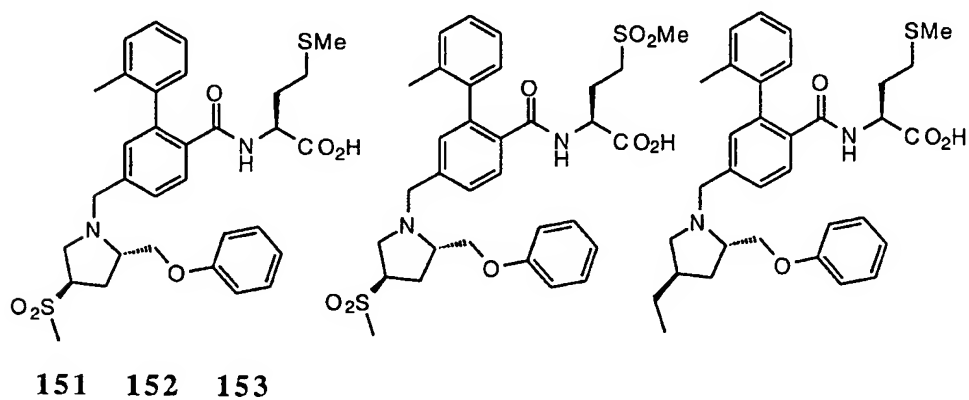
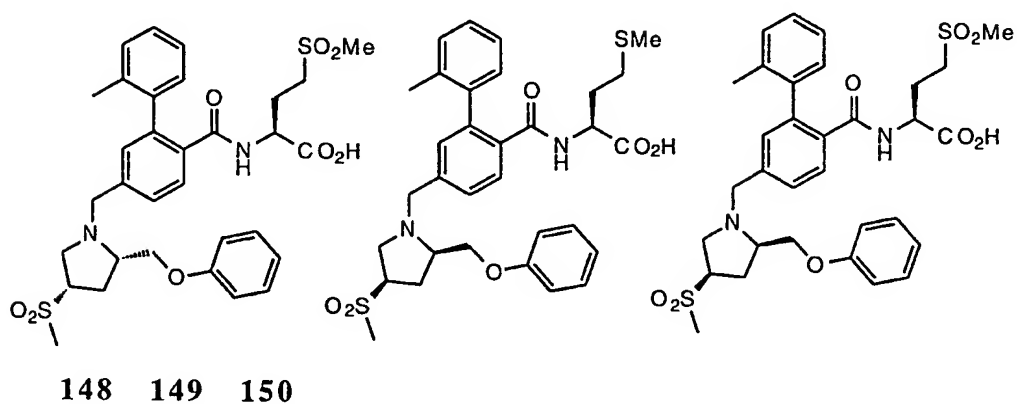


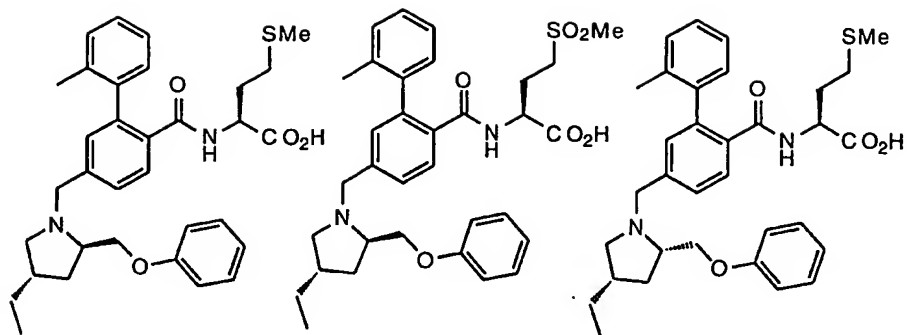
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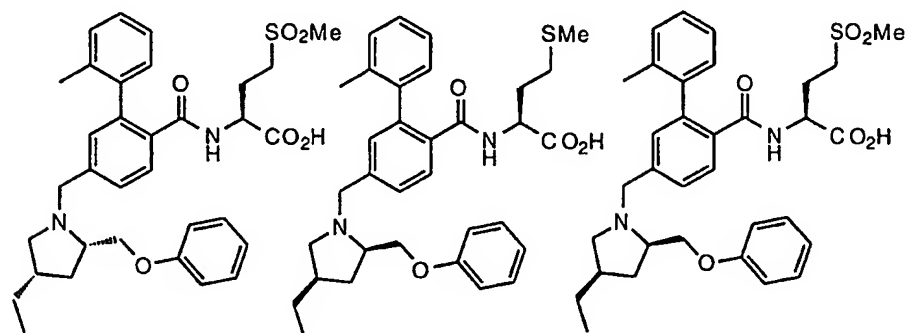
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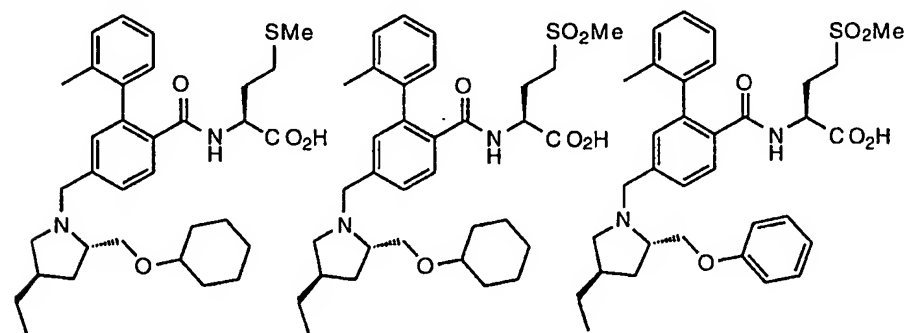


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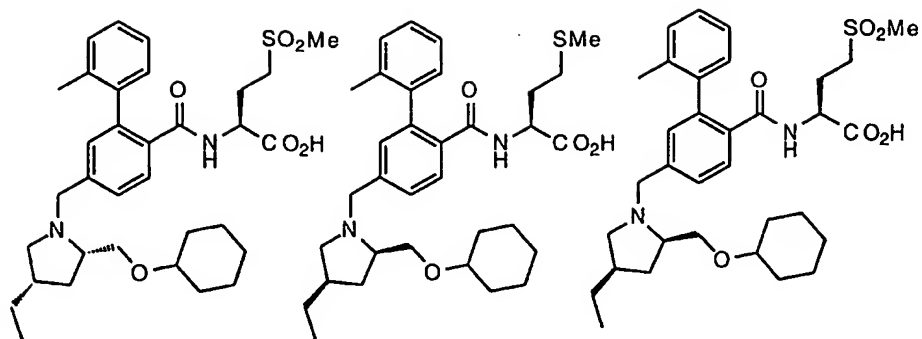


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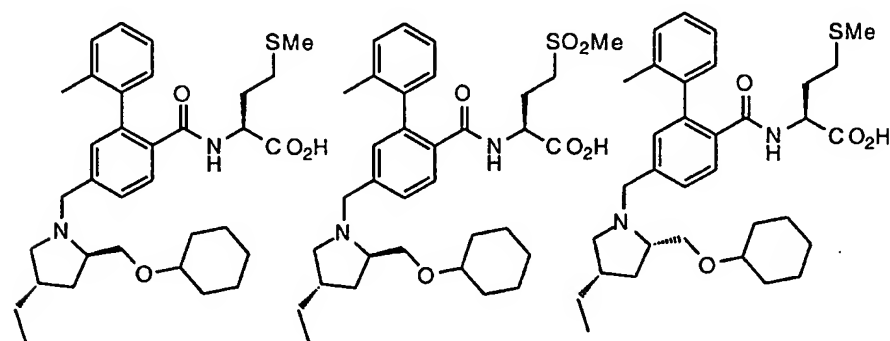
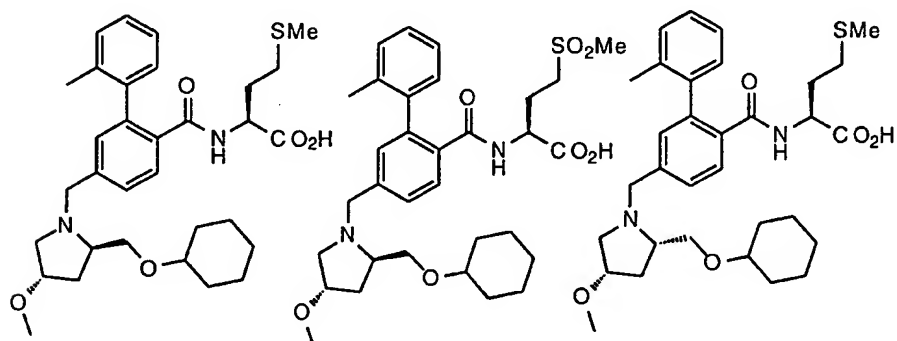


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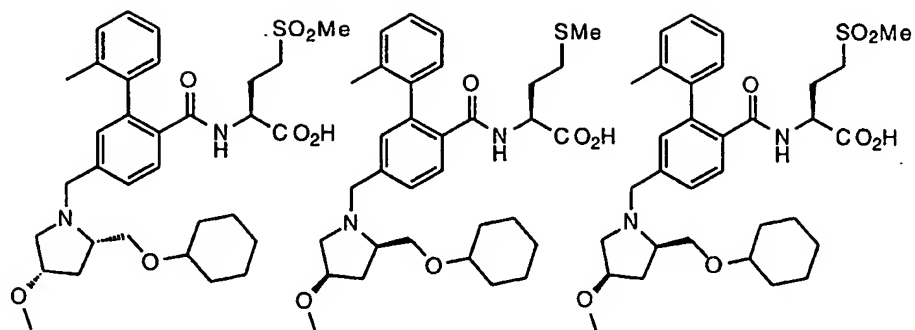
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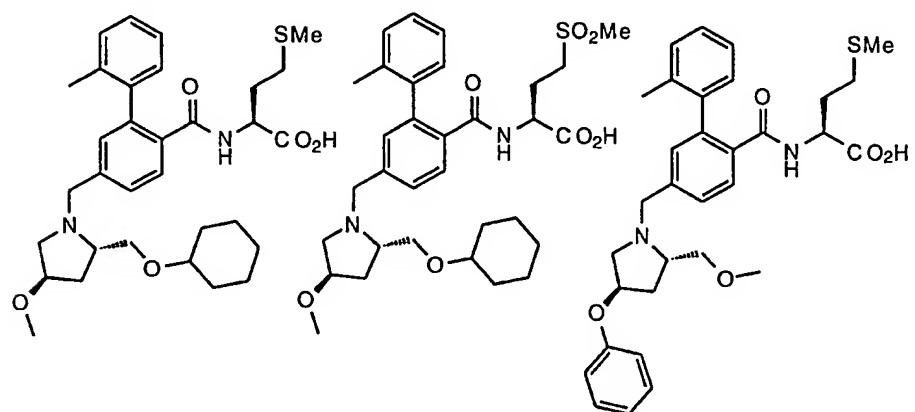
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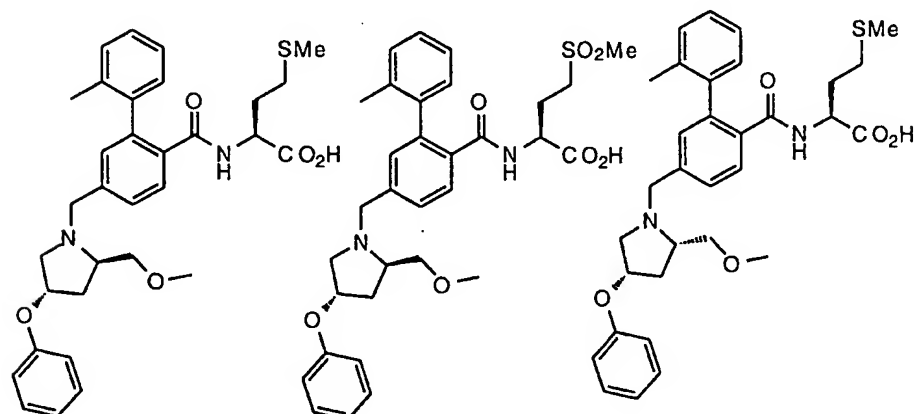


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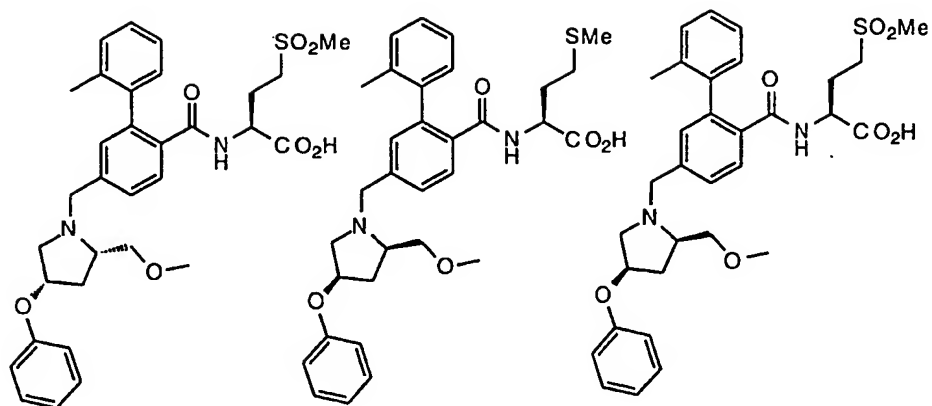
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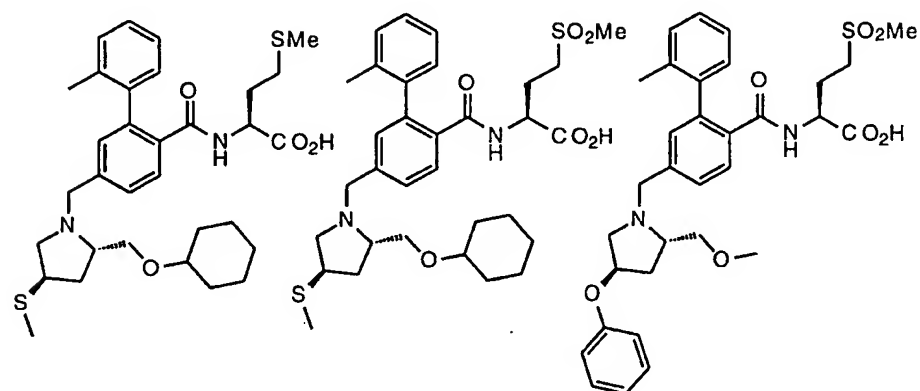


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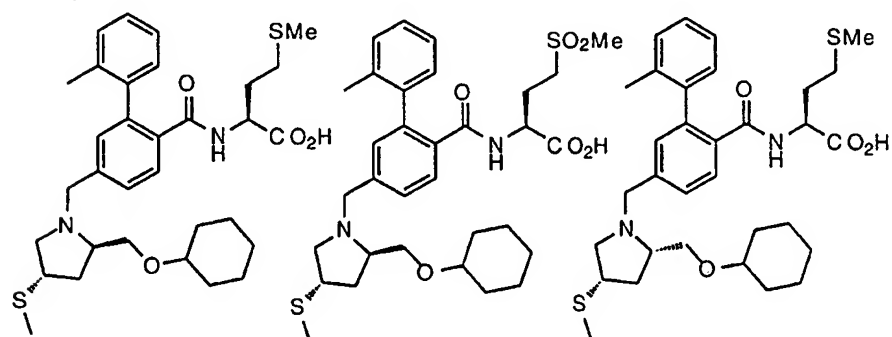


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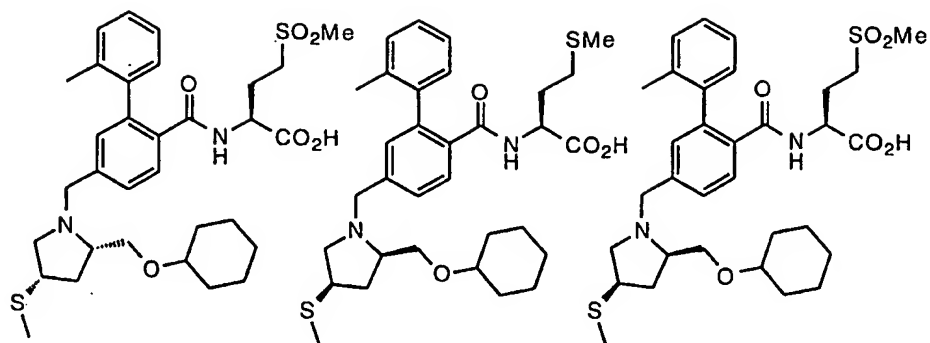


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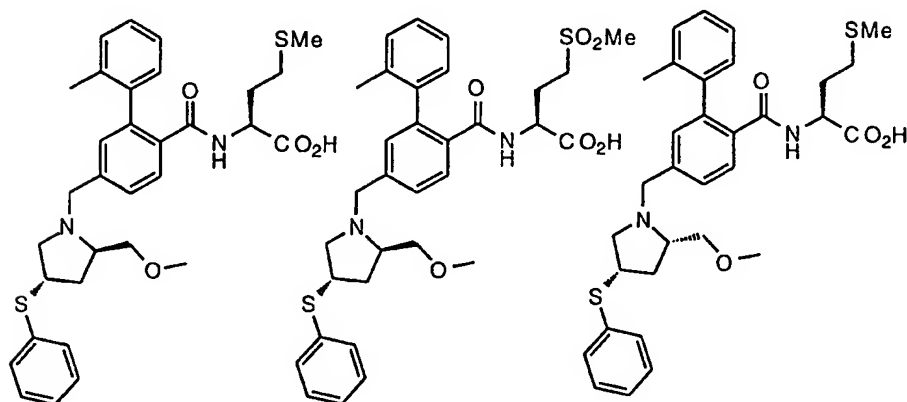


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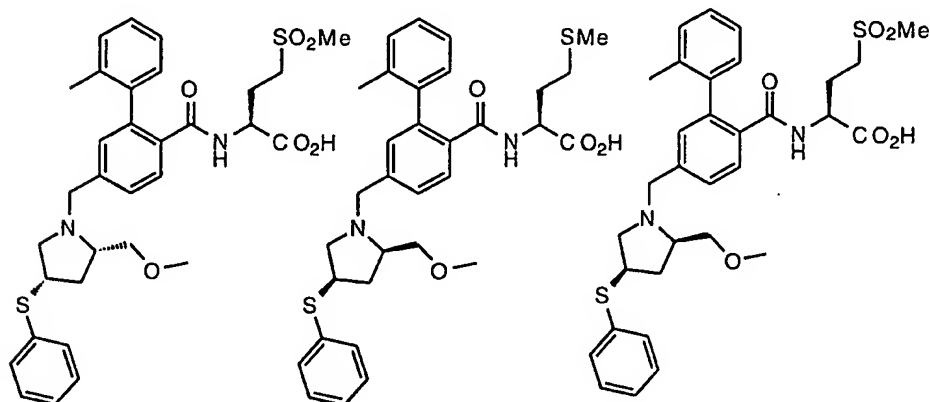
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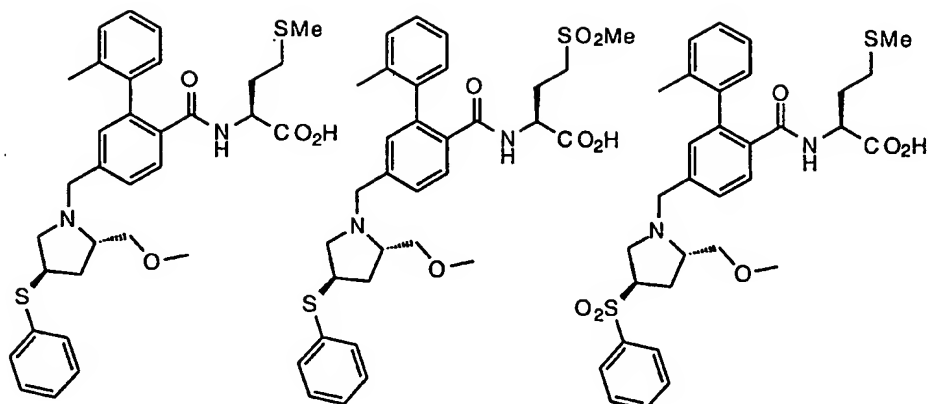


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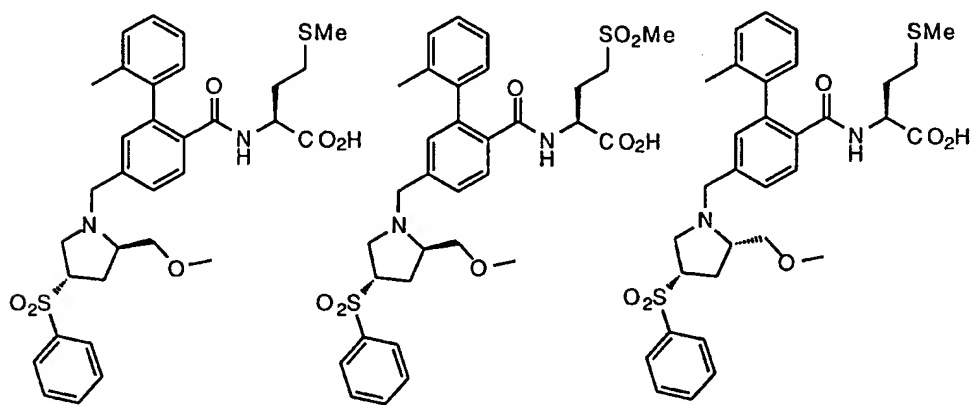


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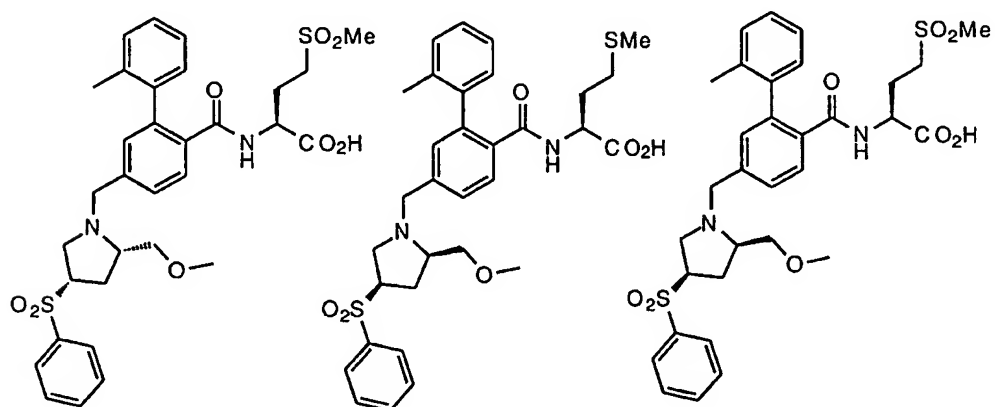


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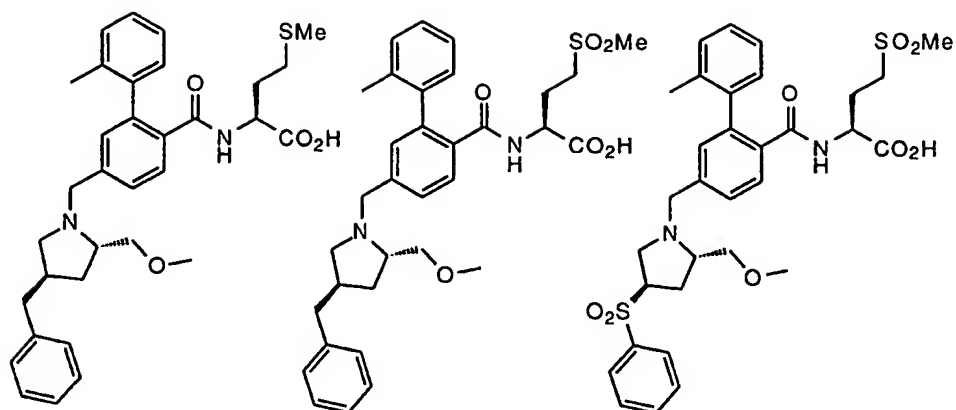


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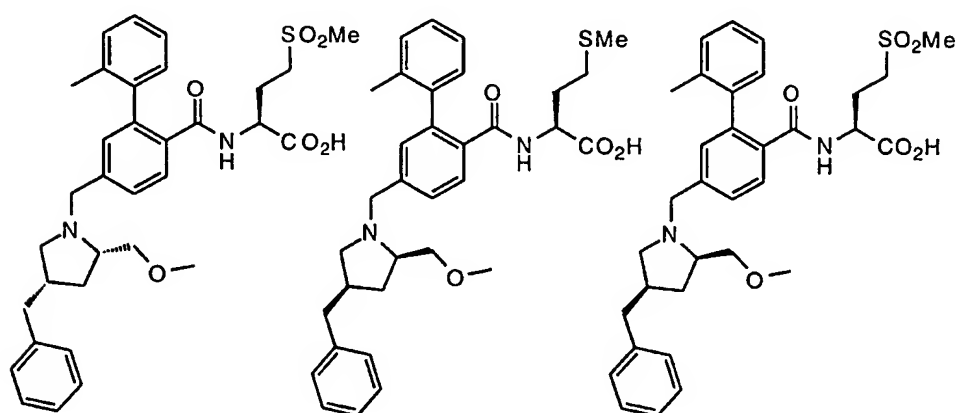
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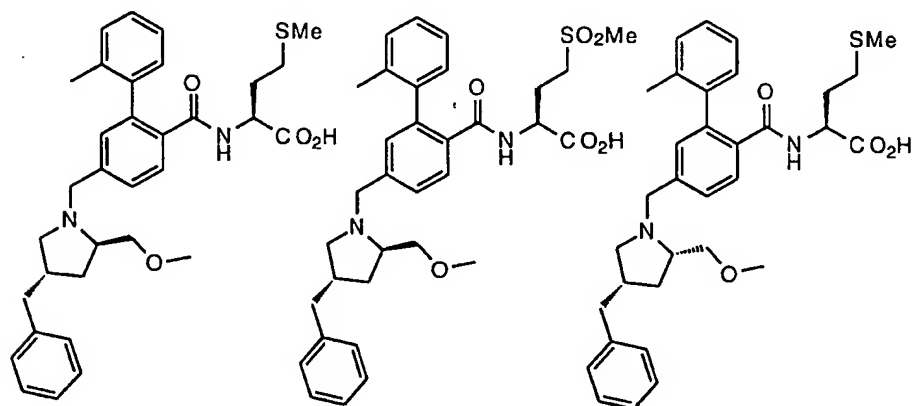


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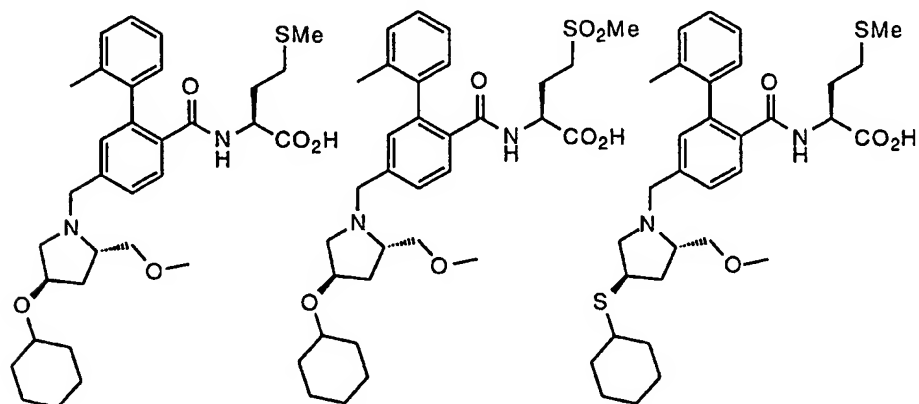
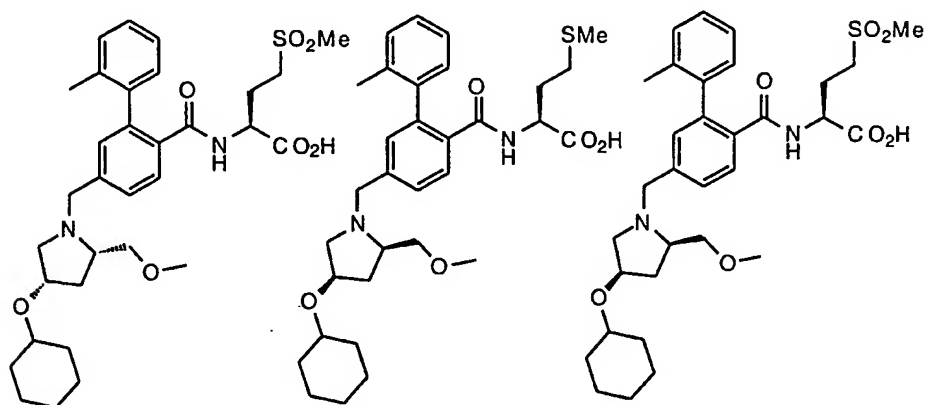
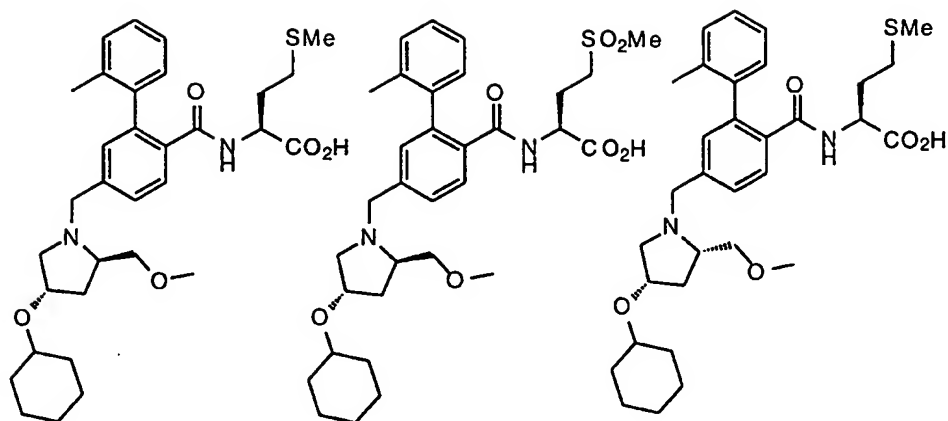


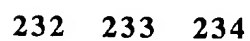
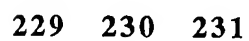
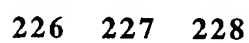
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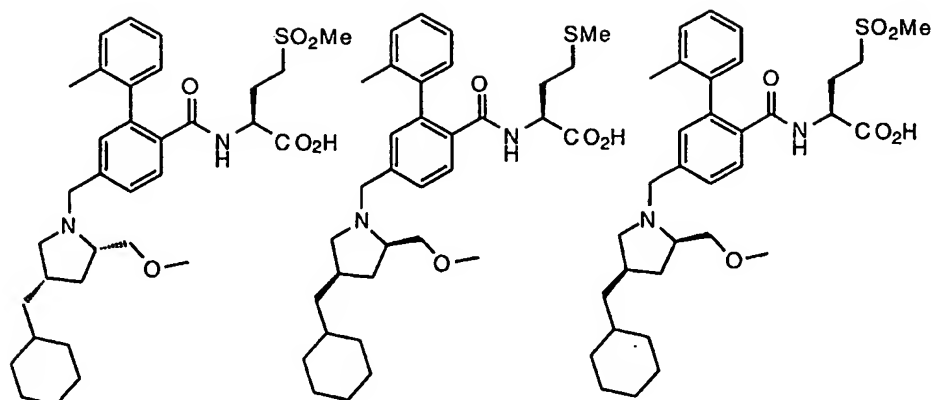


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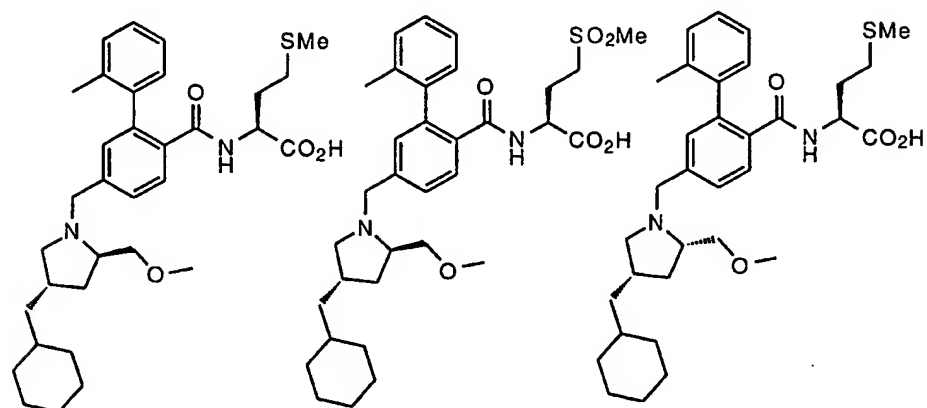






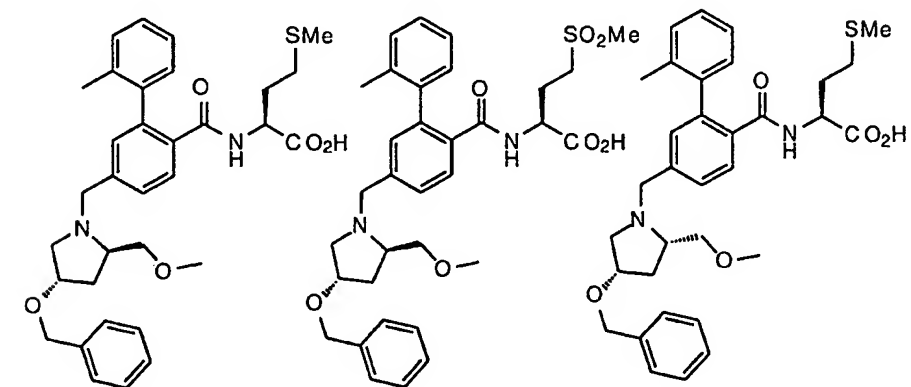
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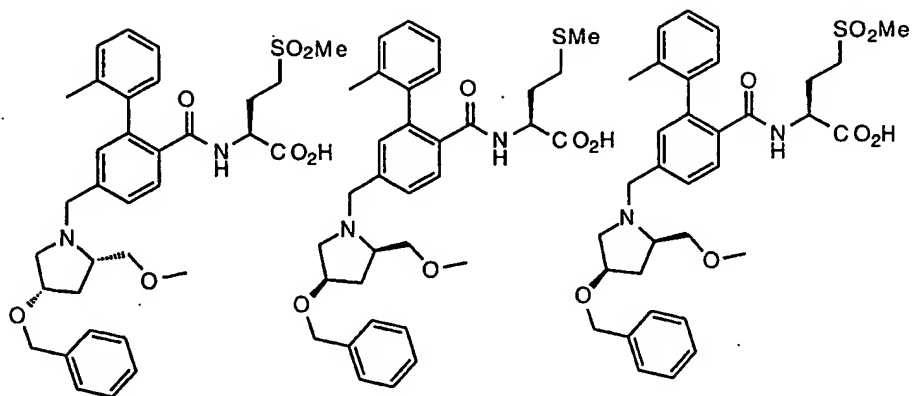


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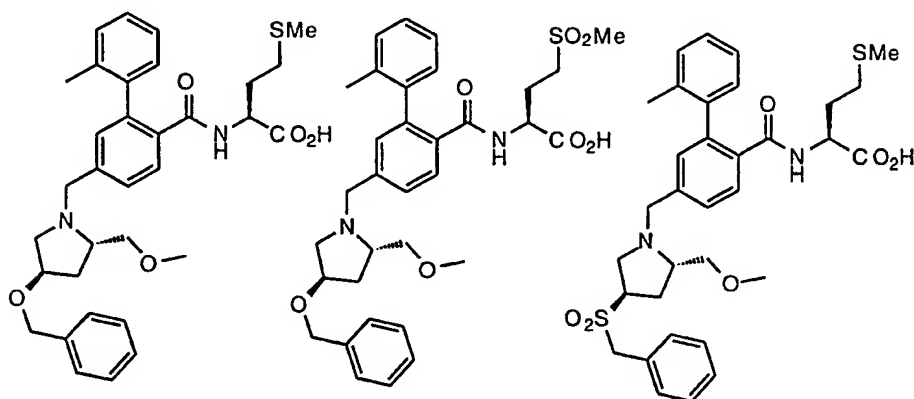


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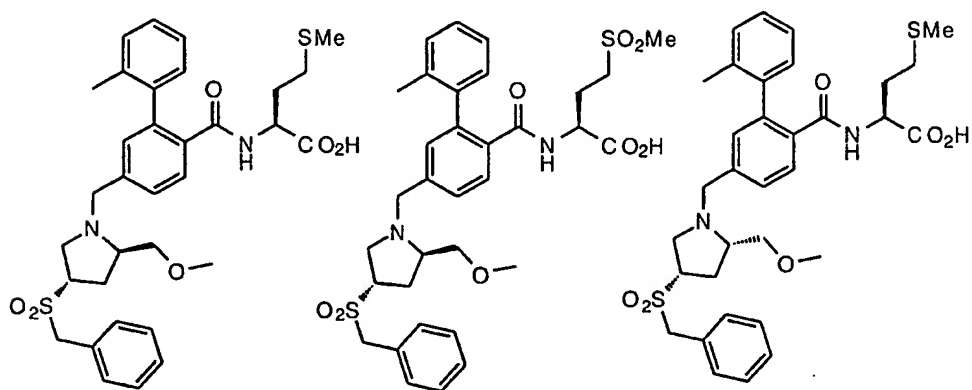


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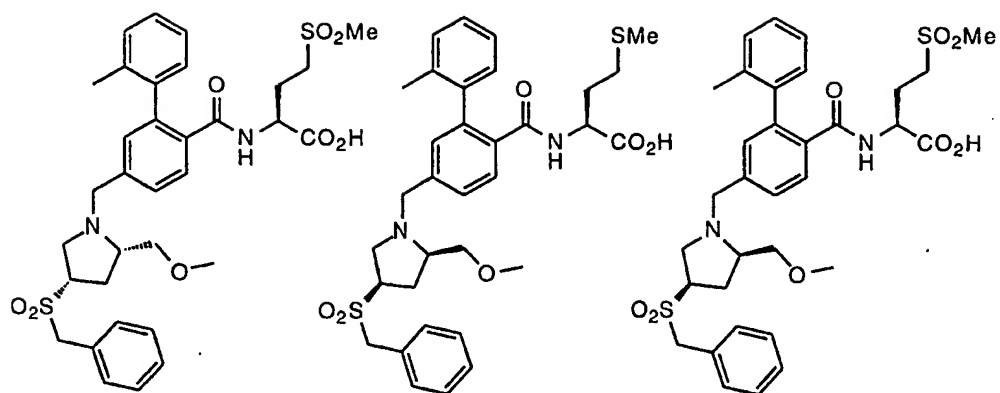


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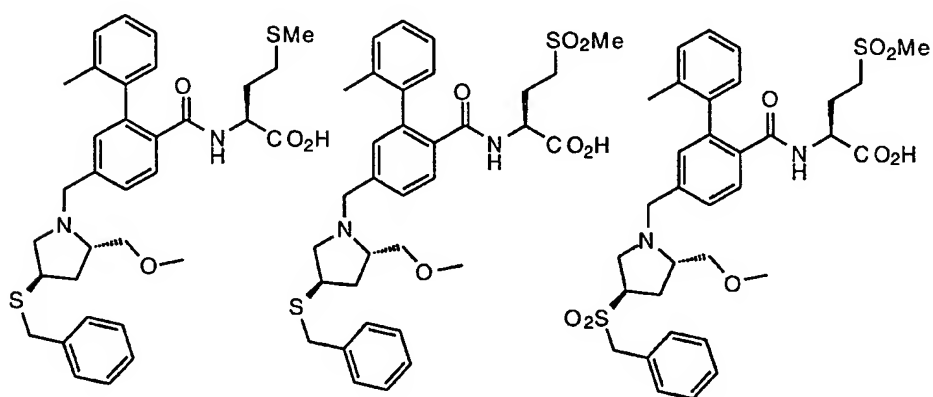
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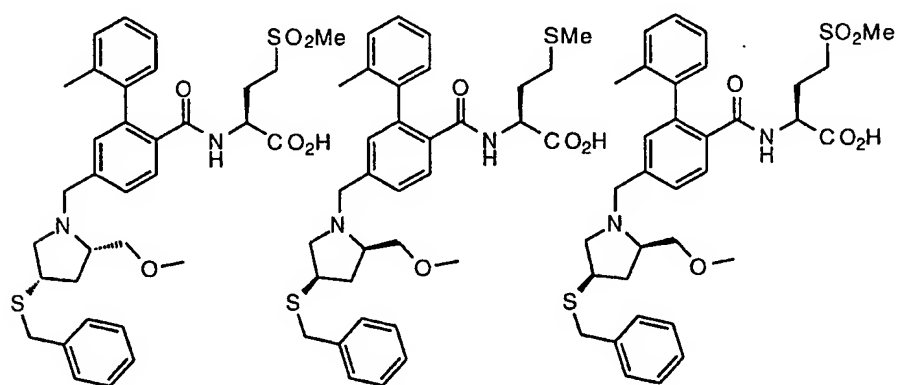


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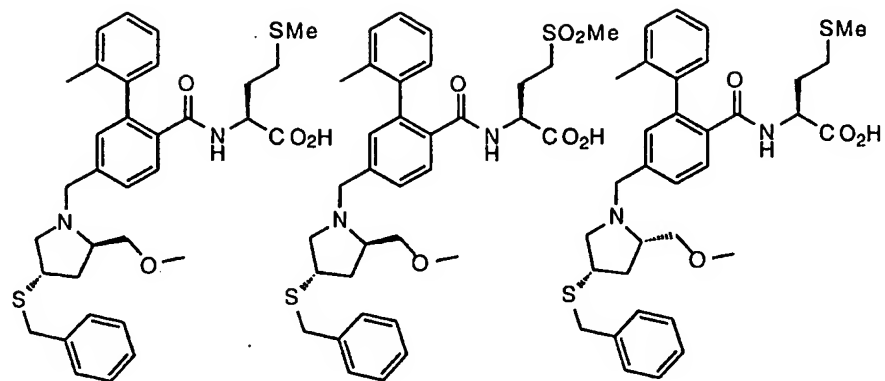


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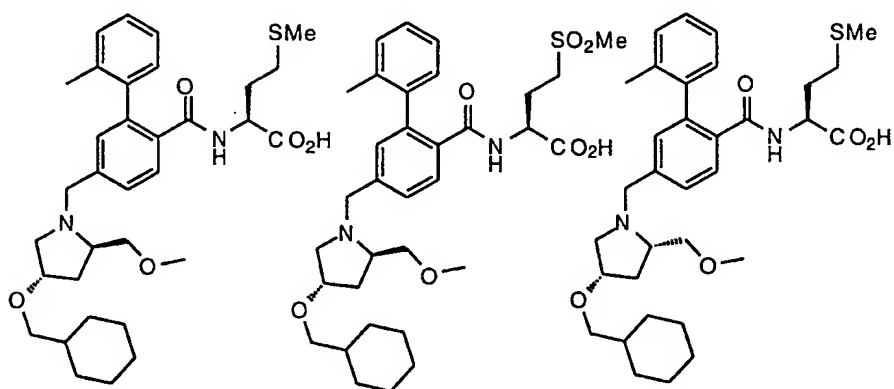


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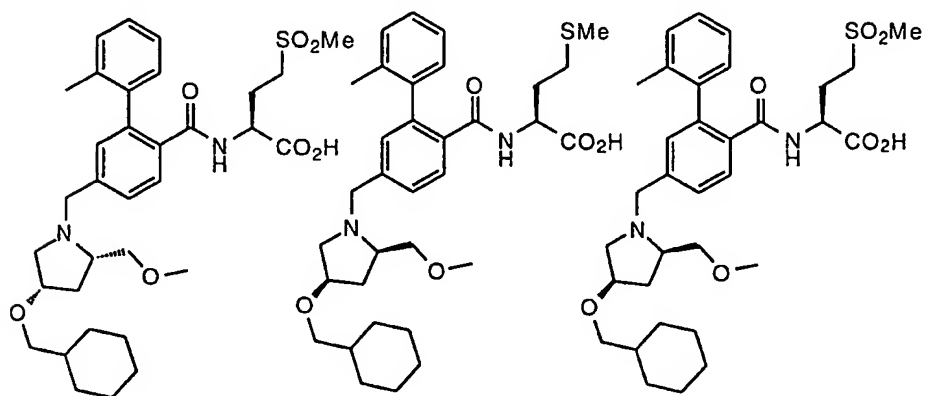


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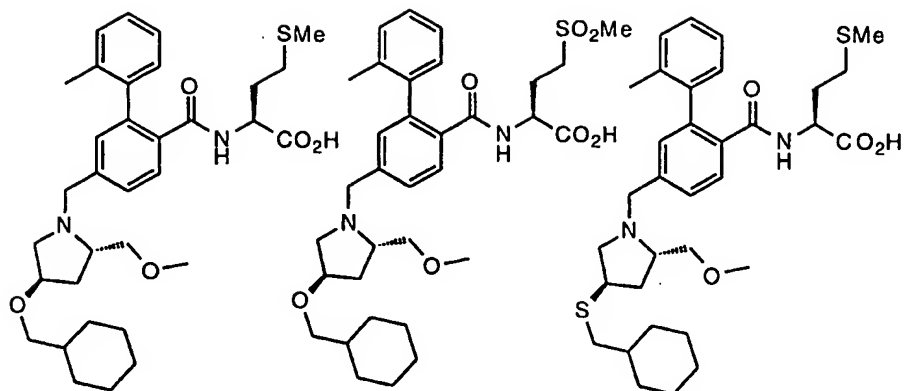
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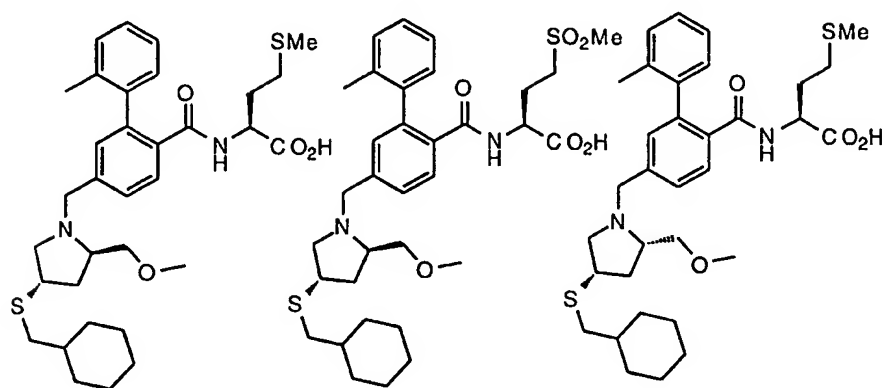


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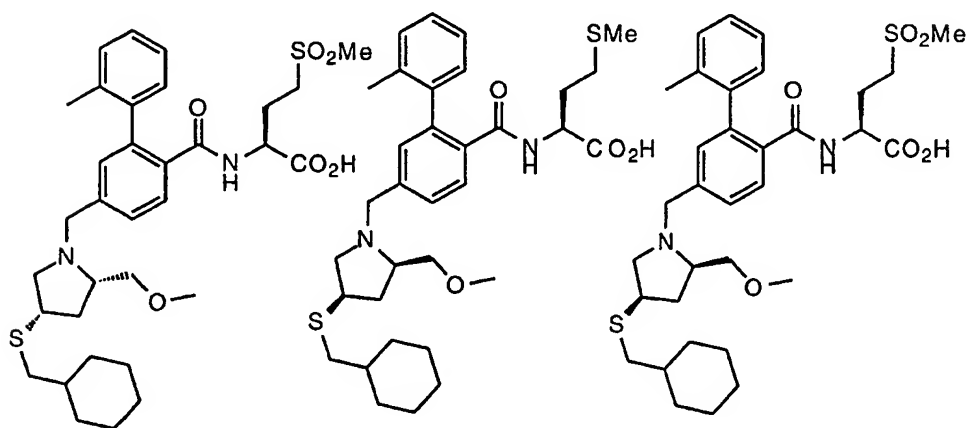


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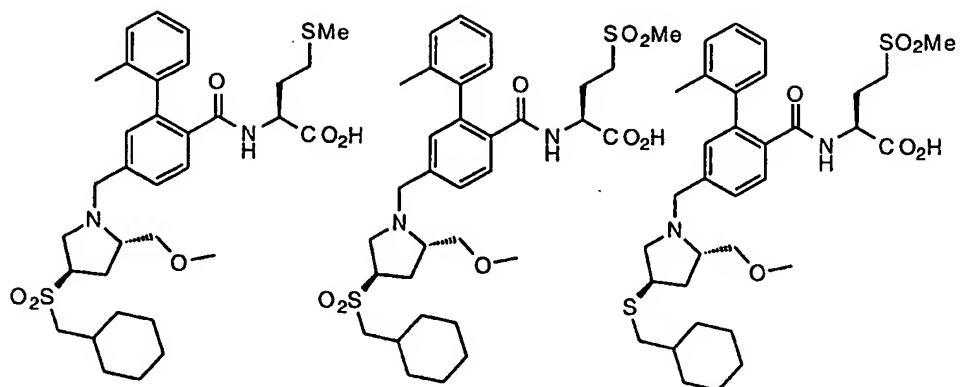


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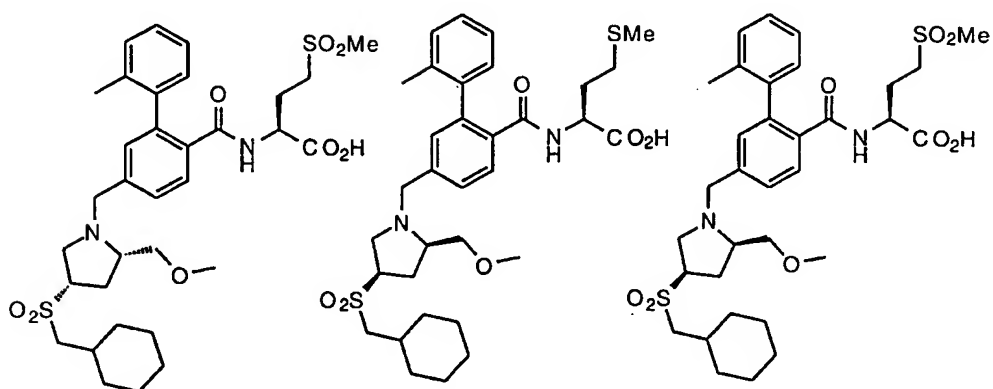


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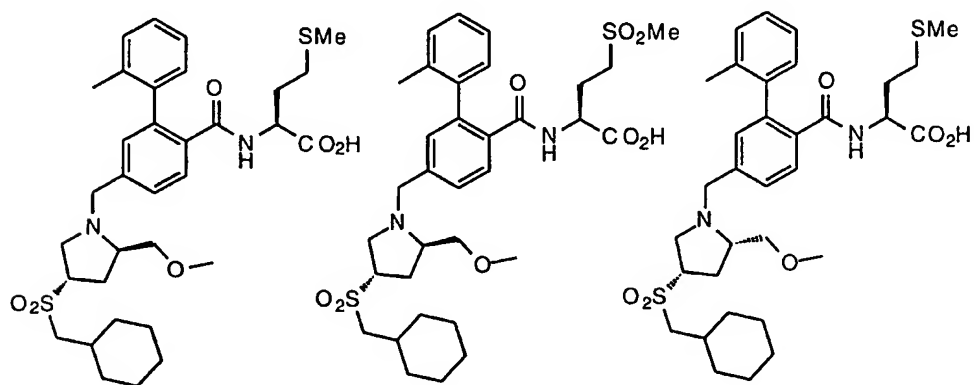
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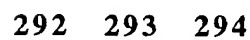
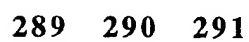


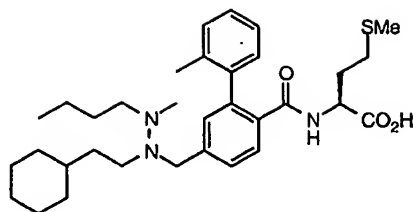
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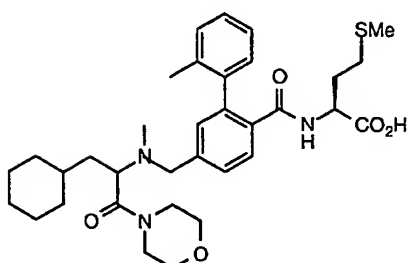
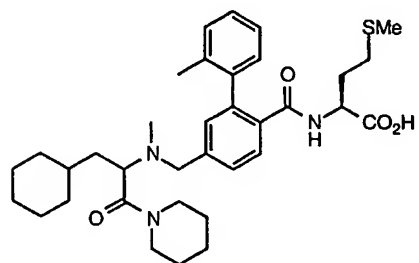
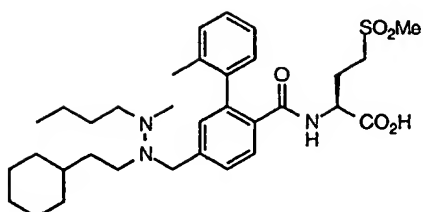


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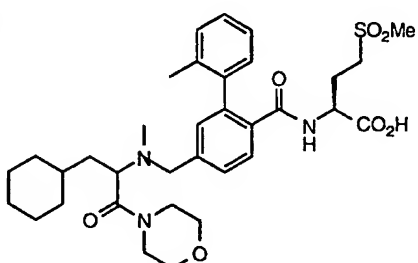
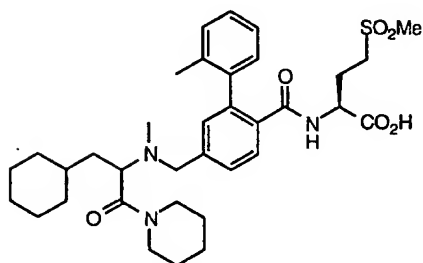


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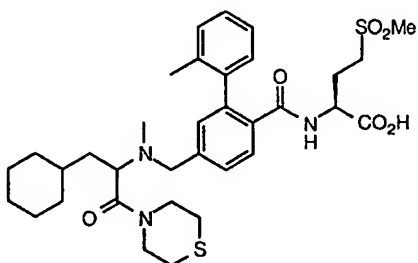
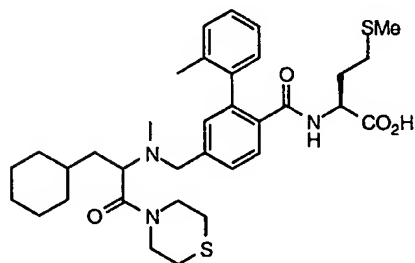


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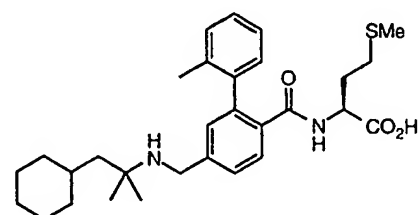
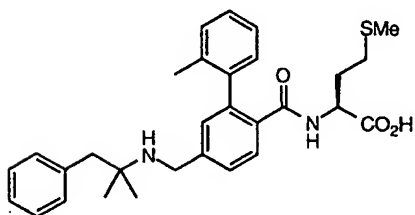


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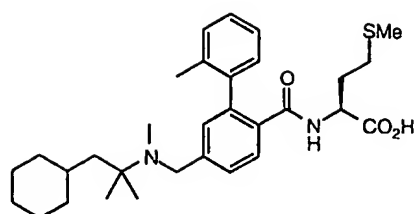
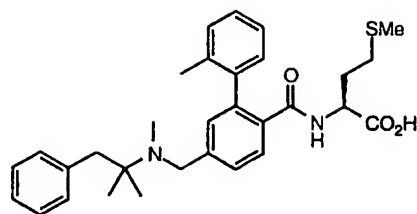
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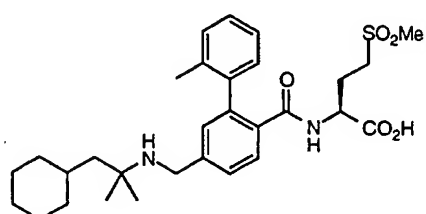
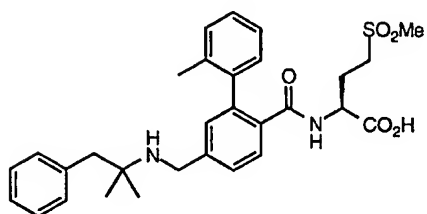


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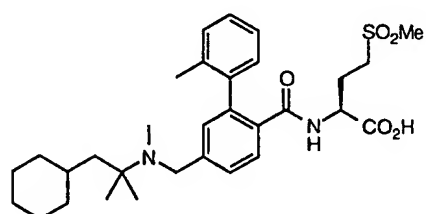
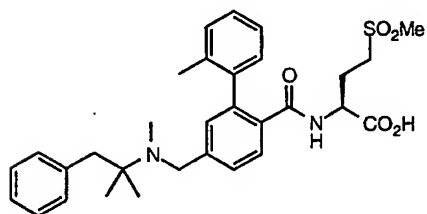


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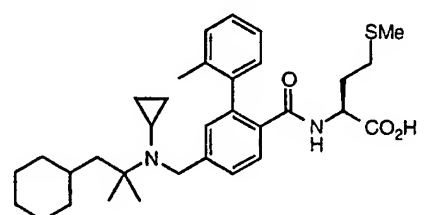
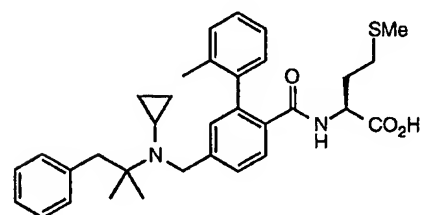


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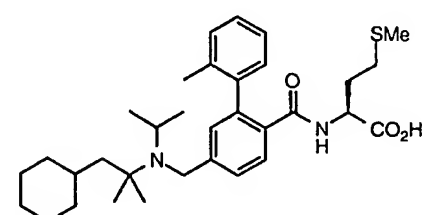
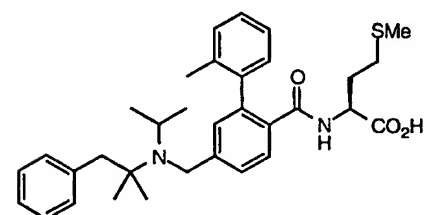


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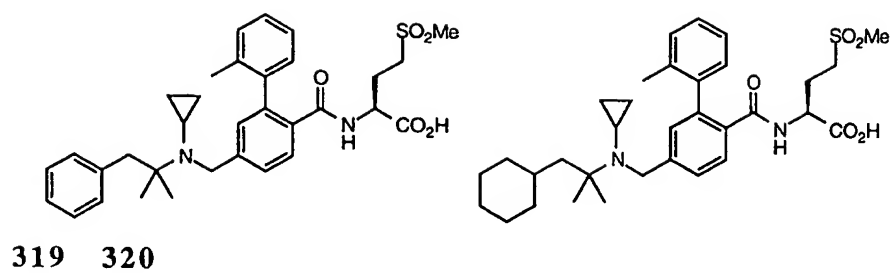
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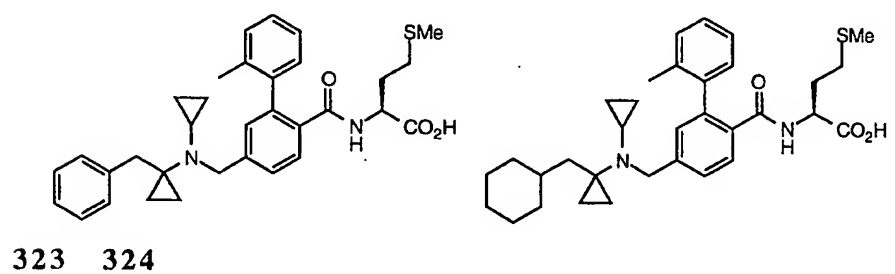
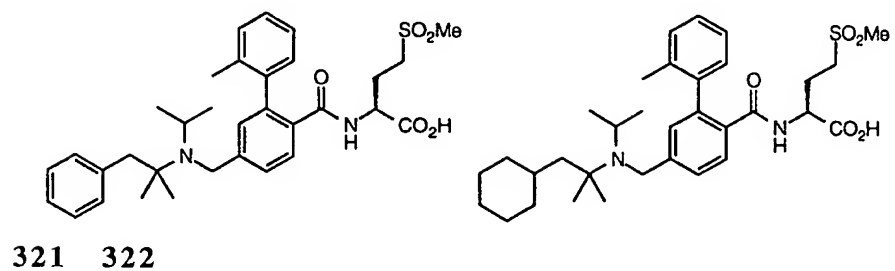
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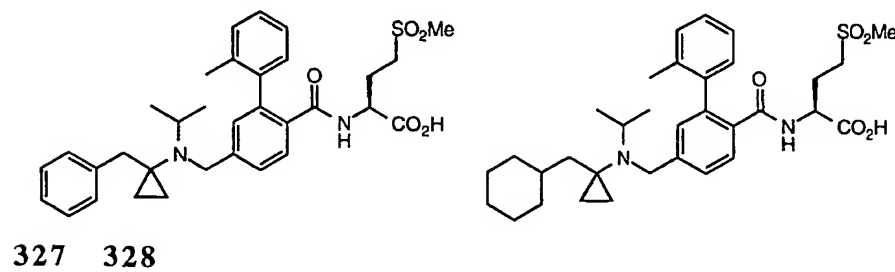
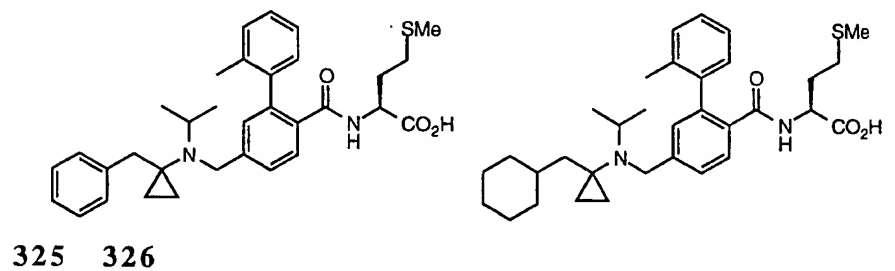
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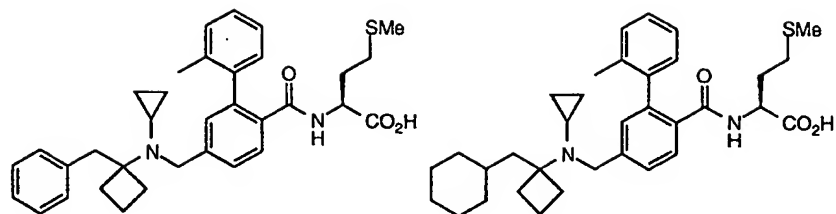
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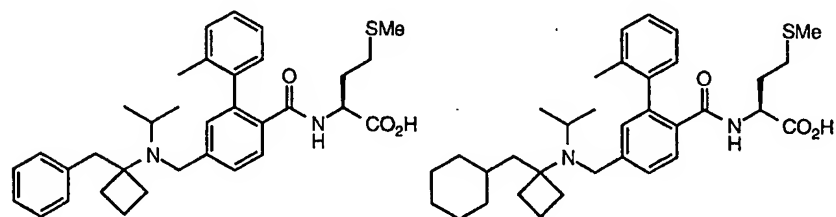
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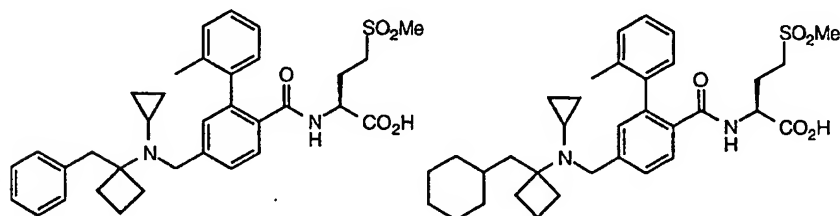
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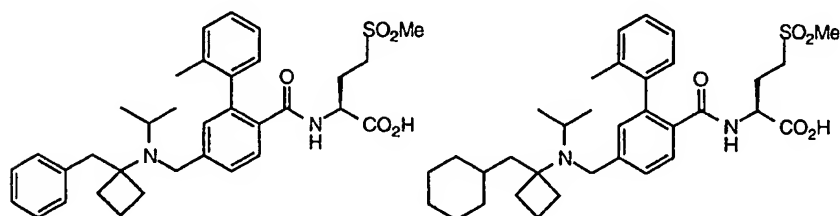
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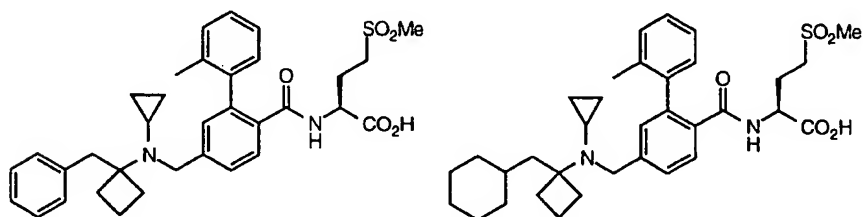
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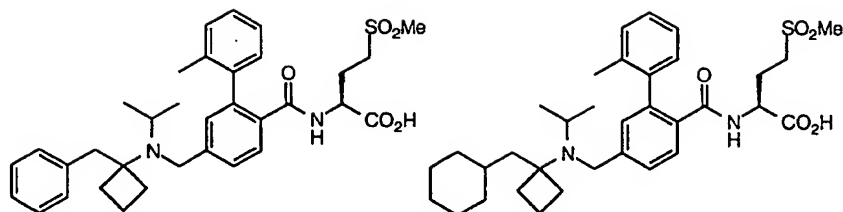
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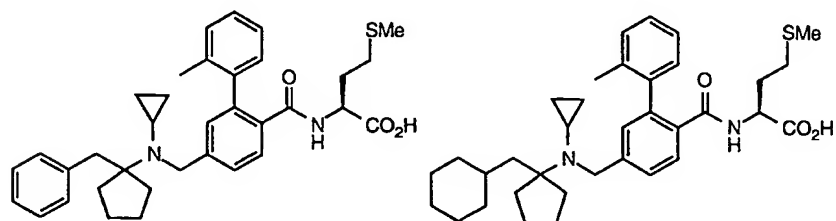
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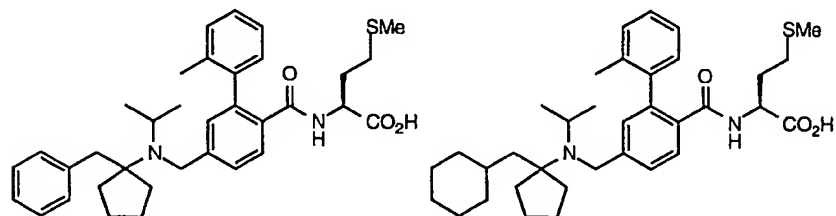
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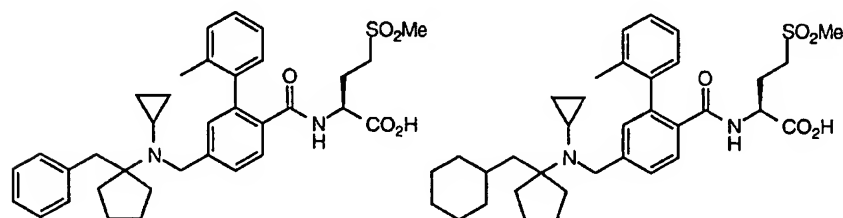
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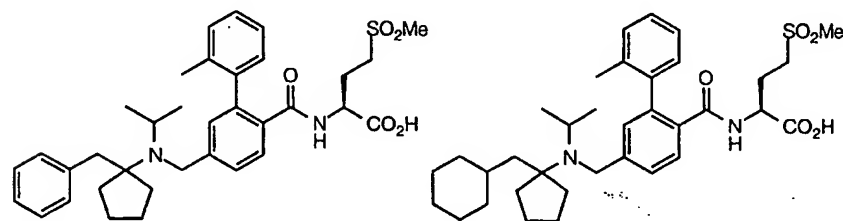
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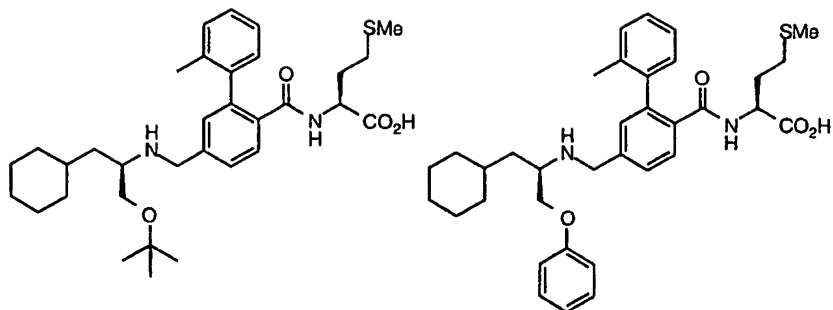
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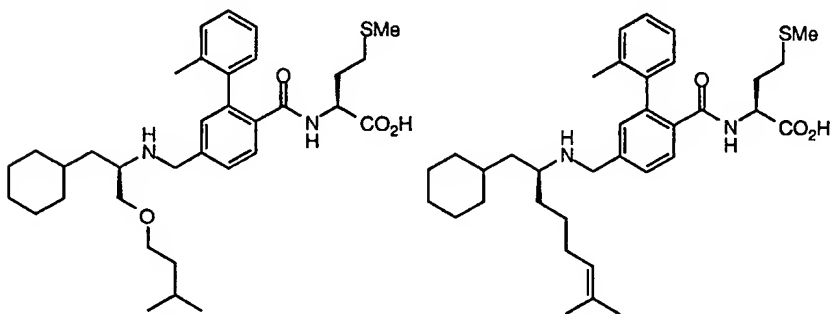
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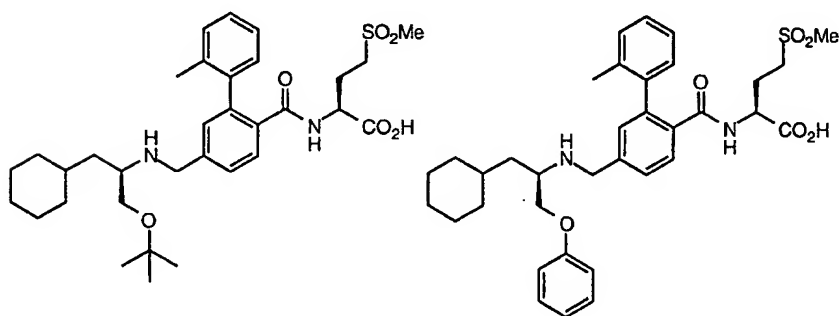
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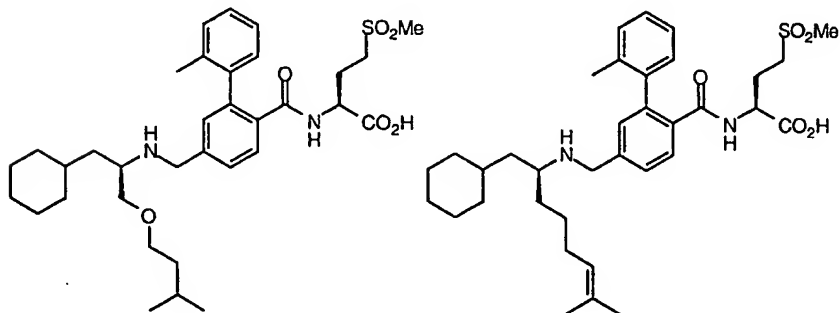
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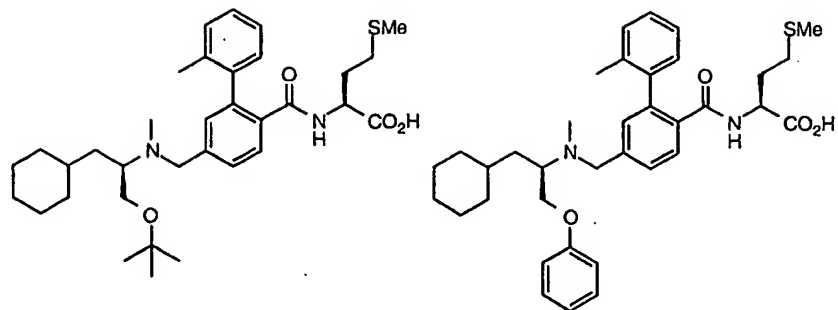
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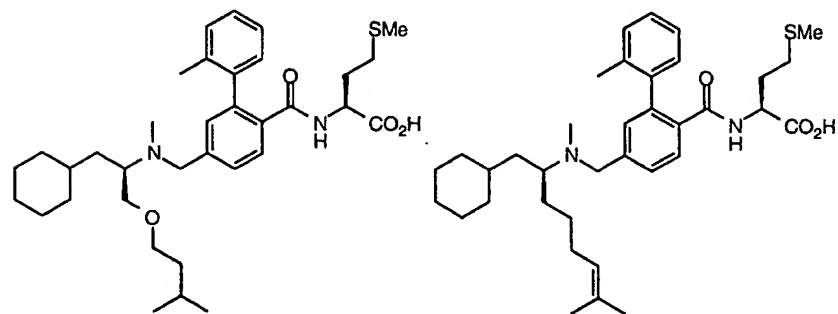


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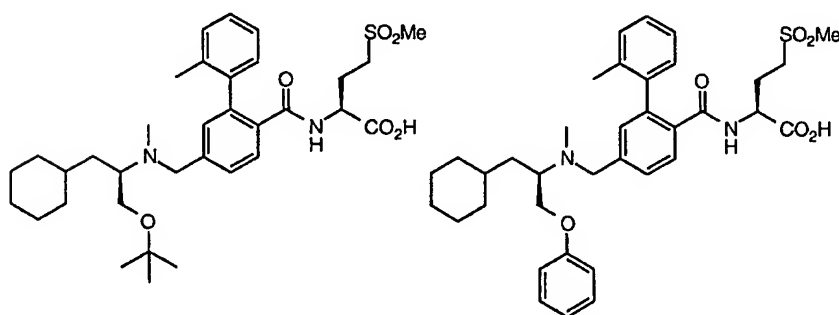


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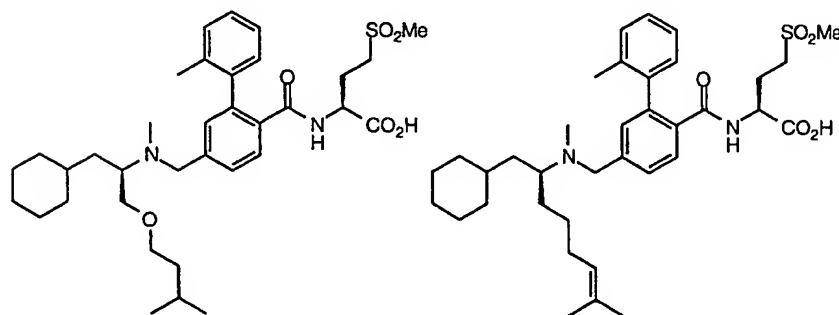


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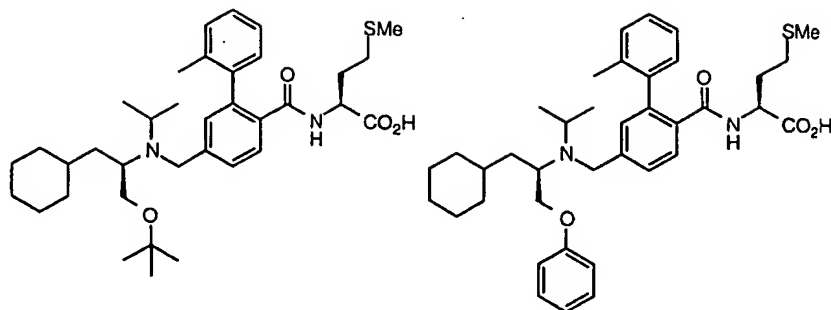


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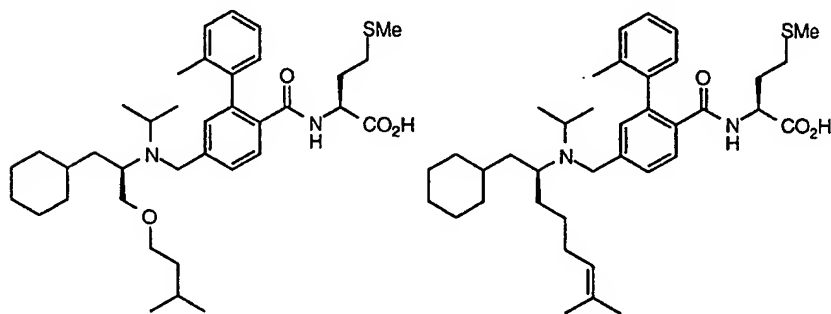


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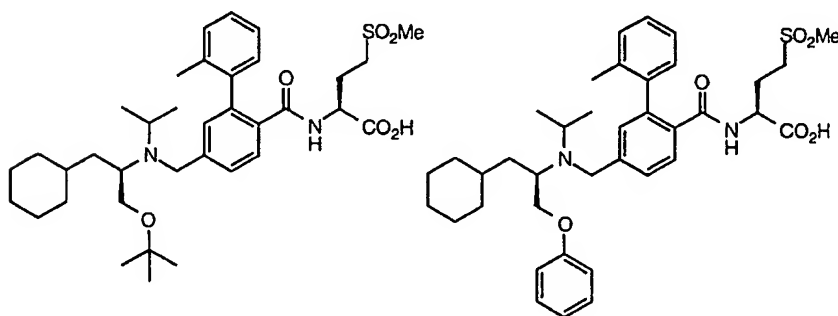
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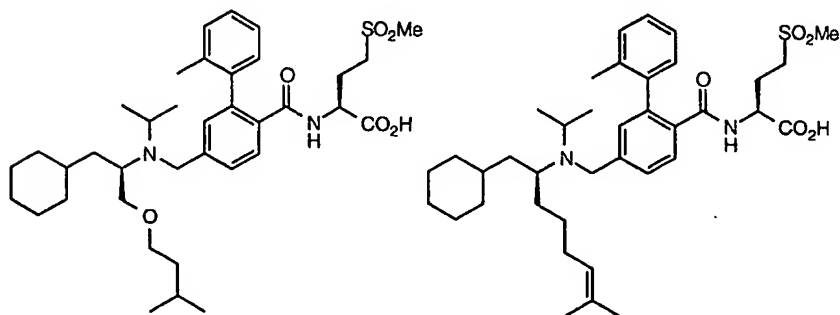


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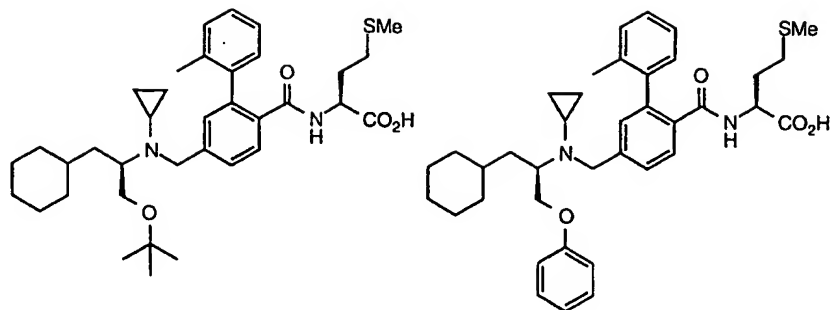


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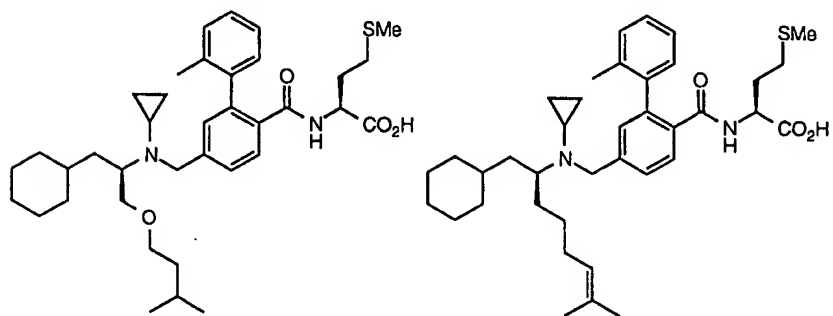


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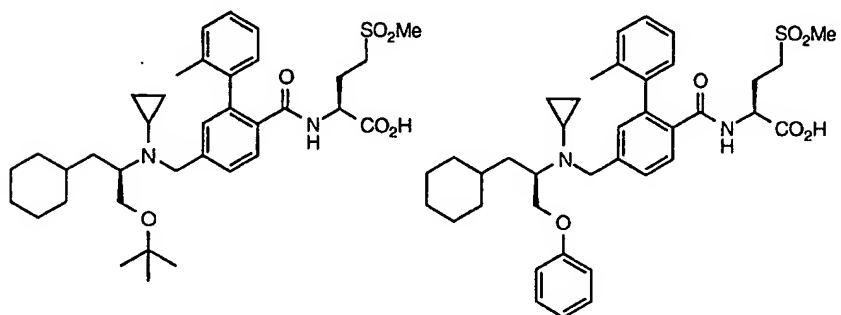
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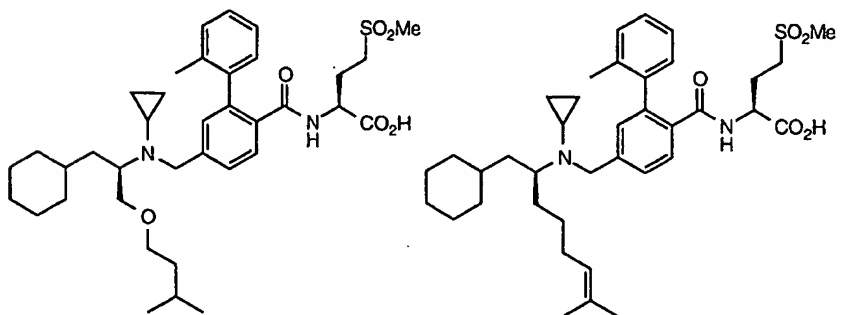
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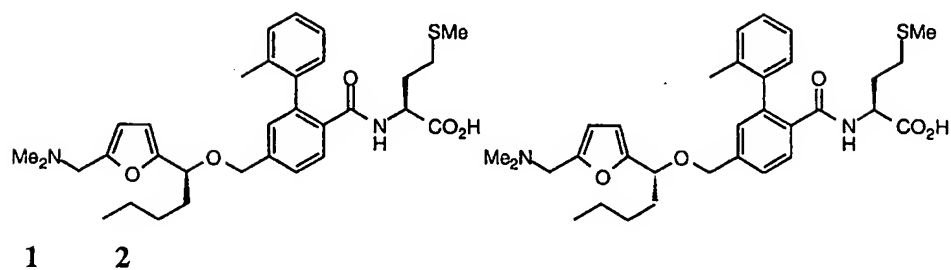
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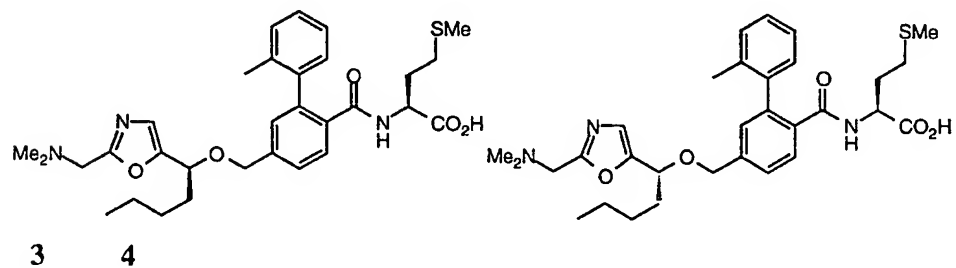
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Table 7. Ethers of the Type A-OL₁

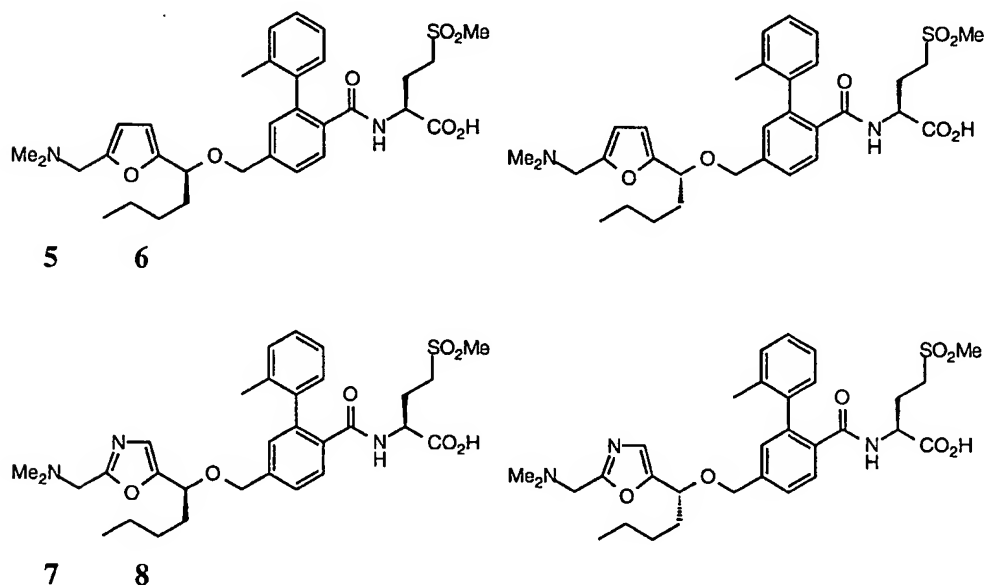
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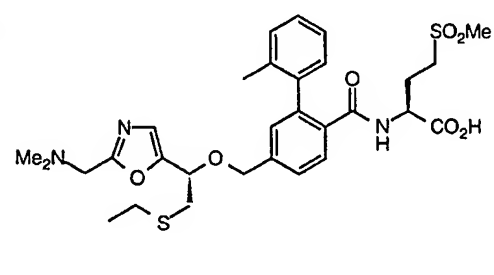
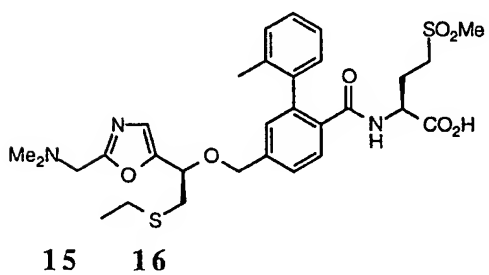
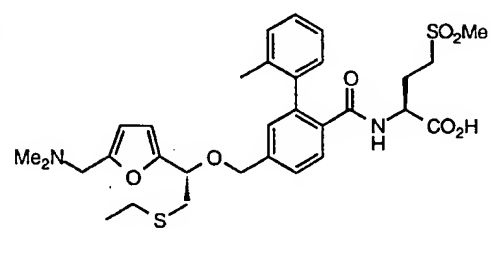
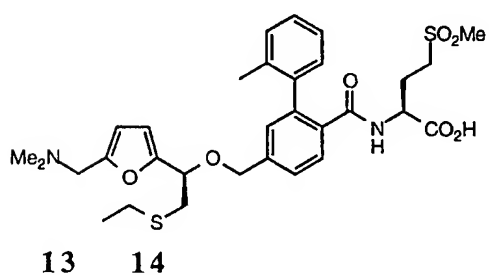
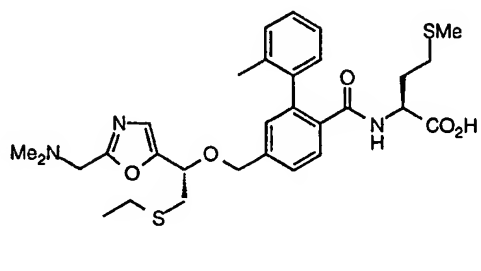
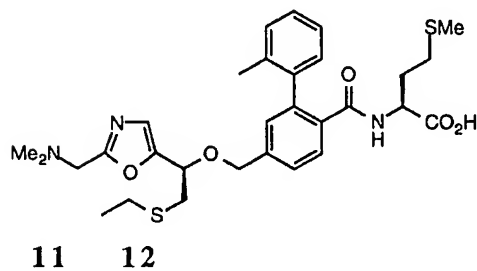
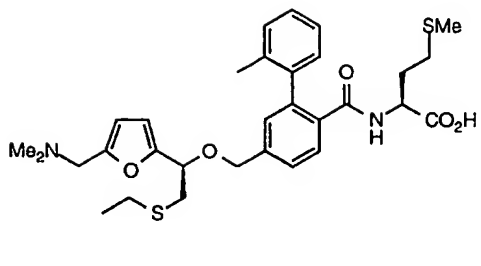
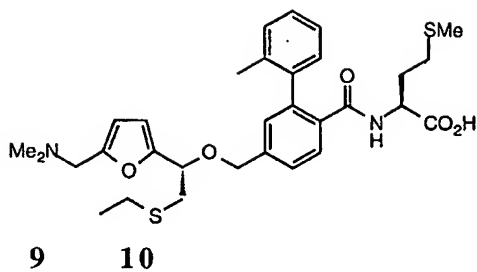


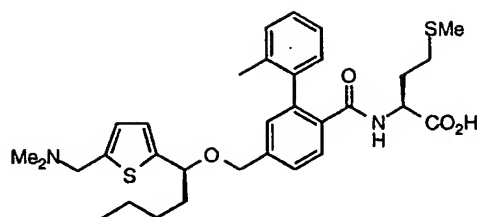
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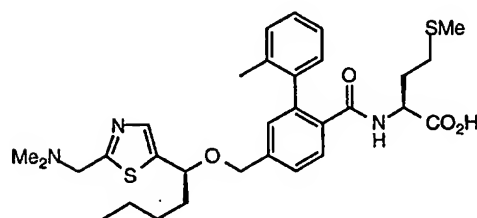
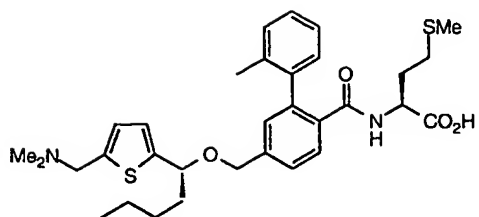
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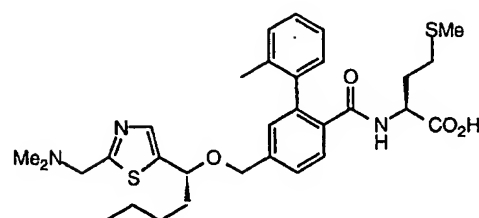




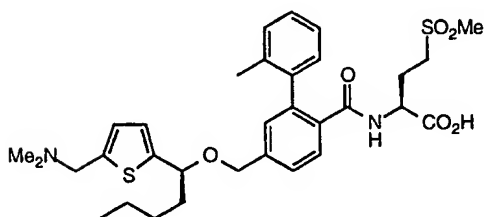
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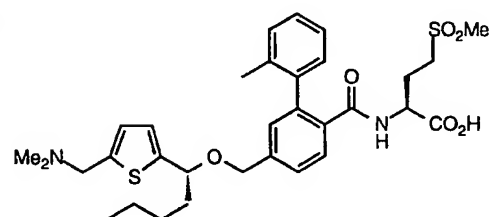
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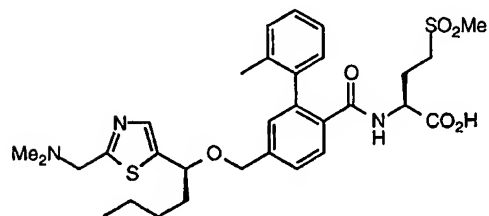
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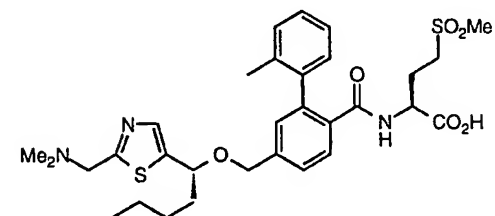
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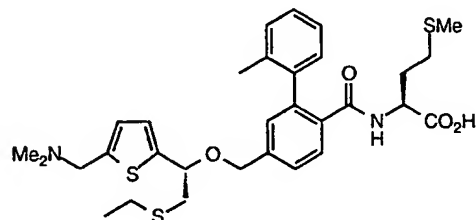
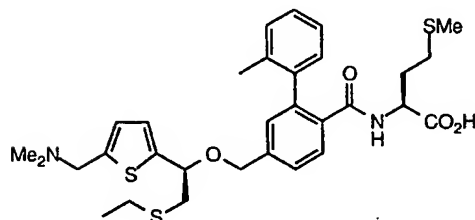
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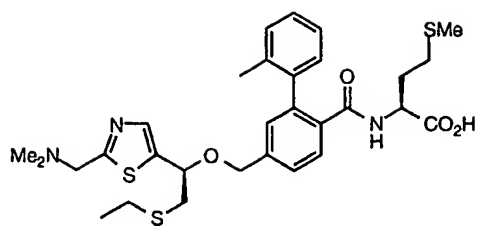
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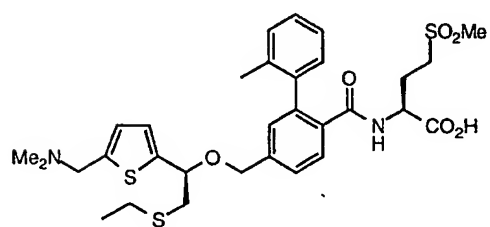
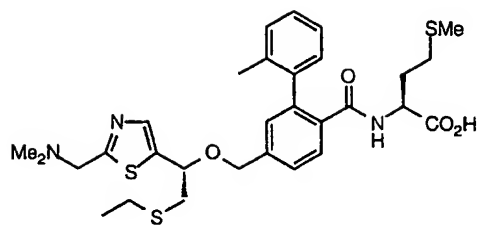


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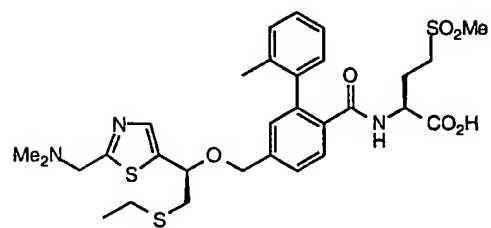
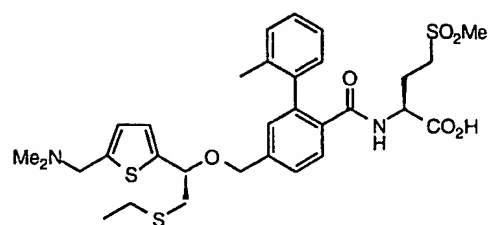
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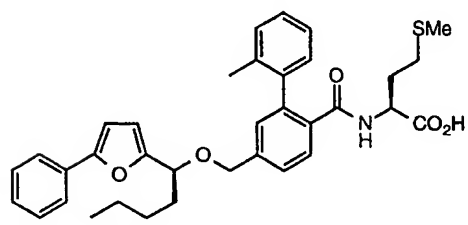
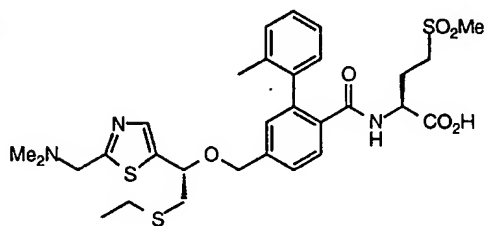
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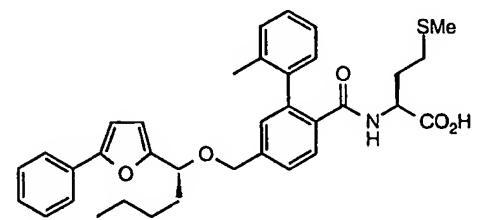
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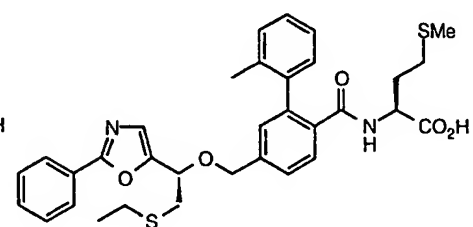
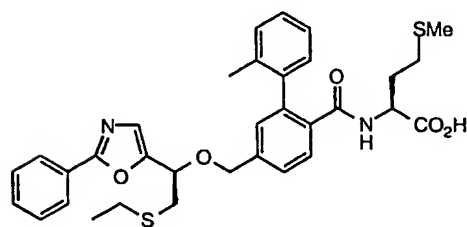
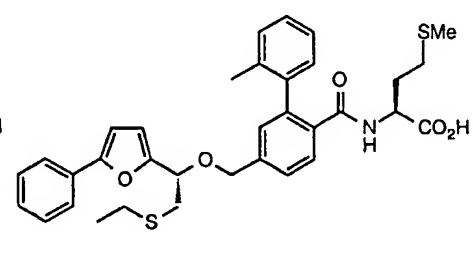
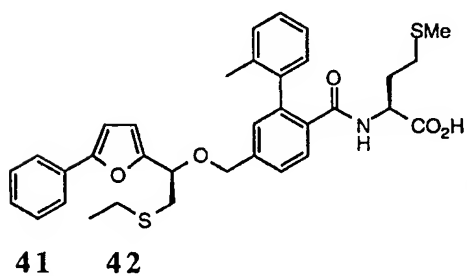
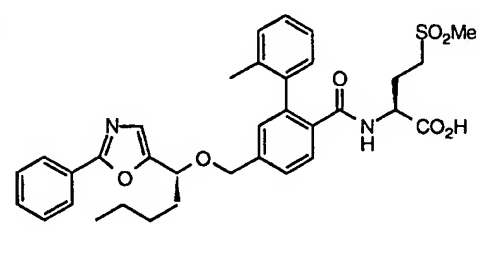
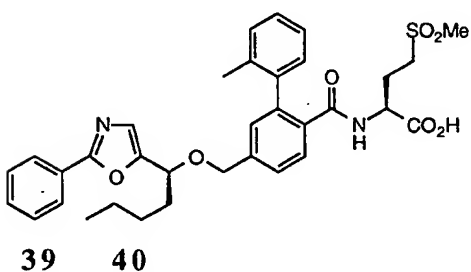
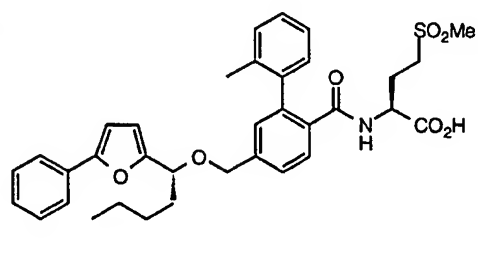
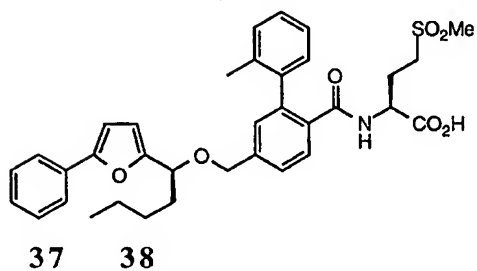
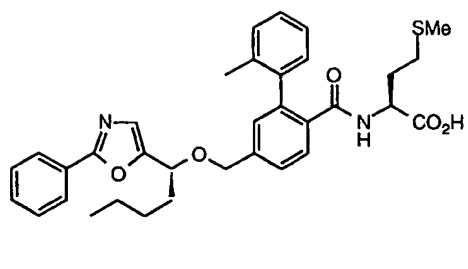
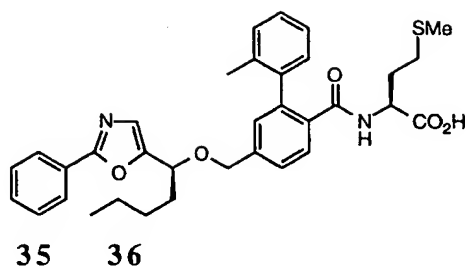
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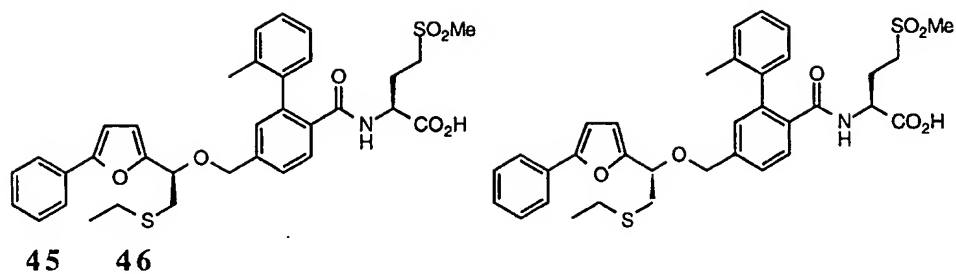
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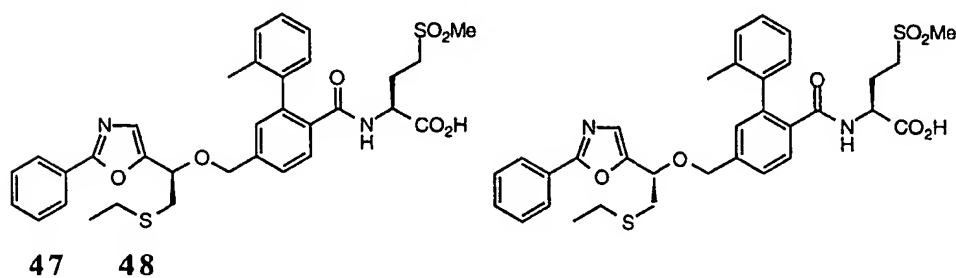


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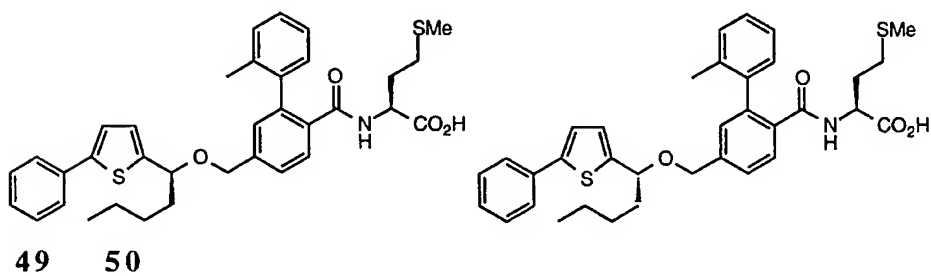
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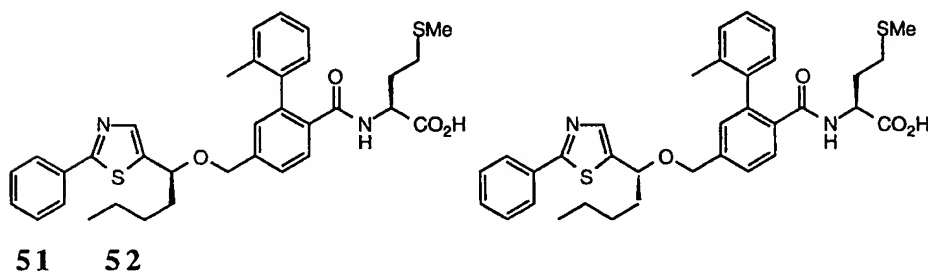
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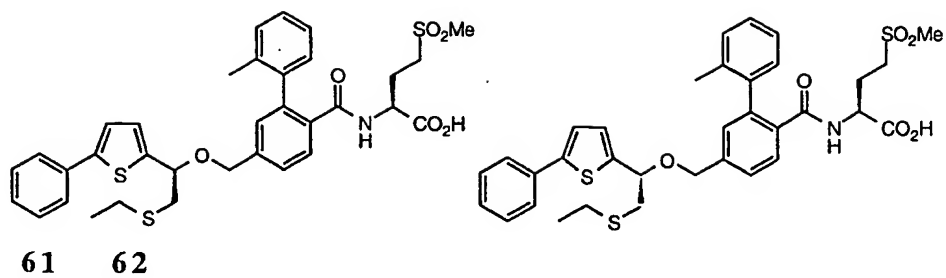


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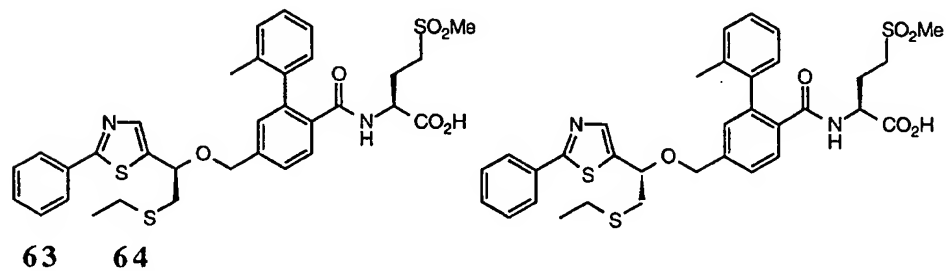


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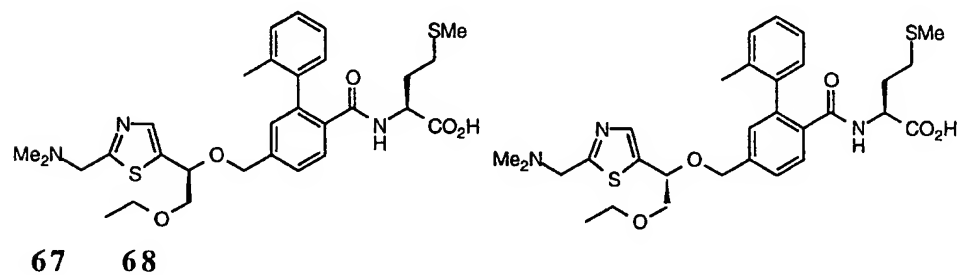
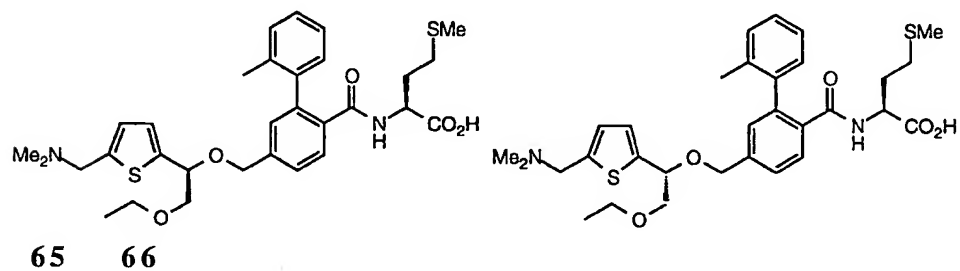




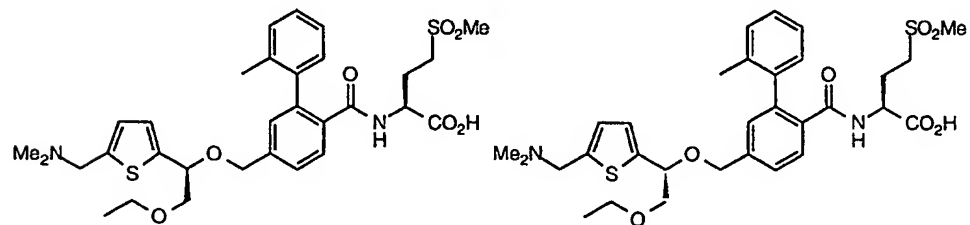
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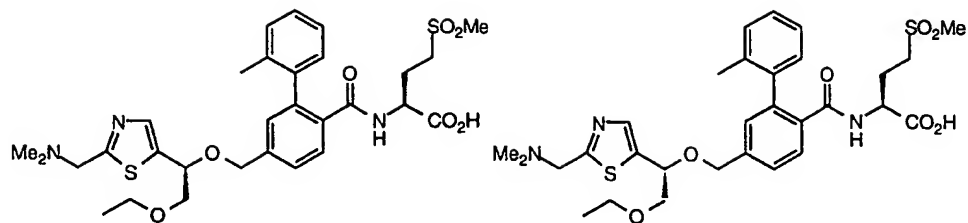
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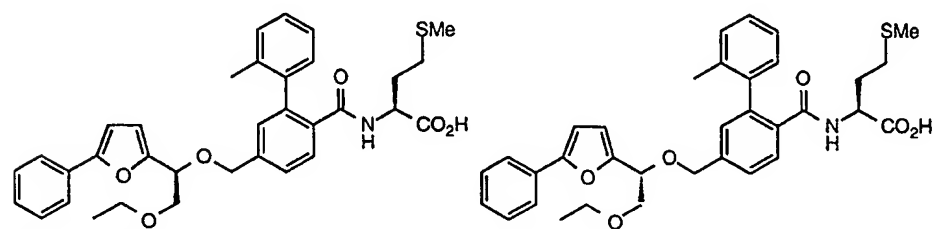


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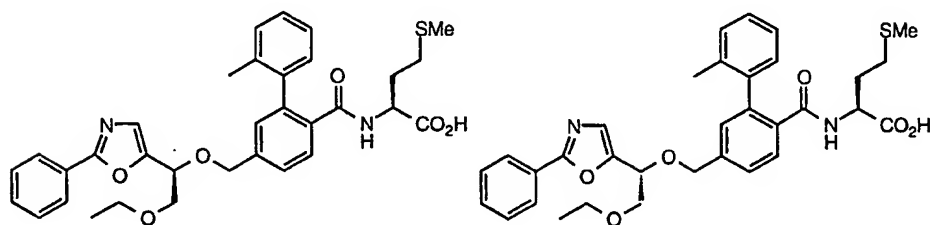
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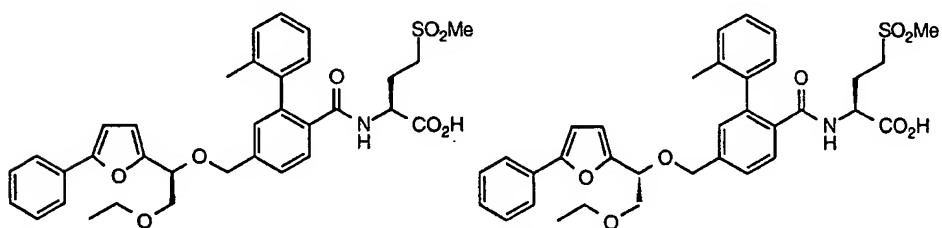


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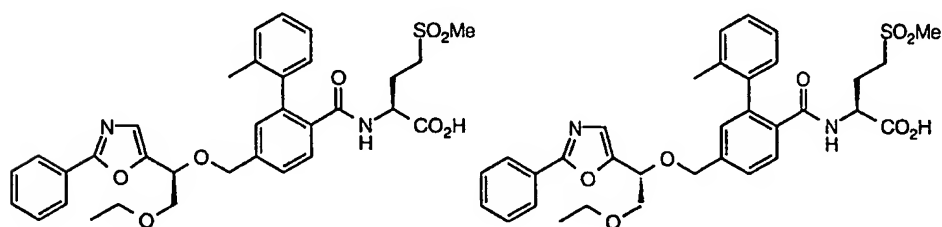


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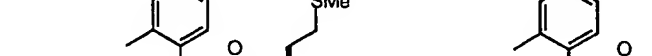
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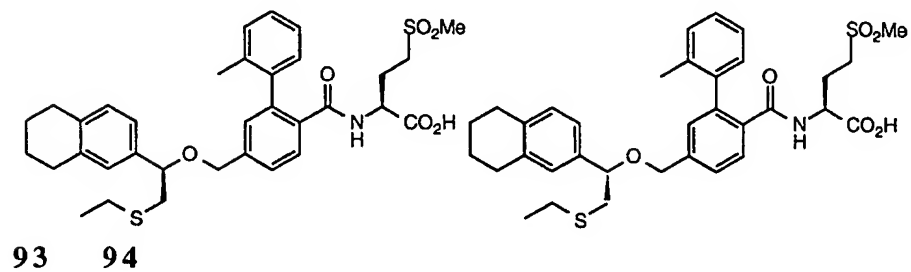
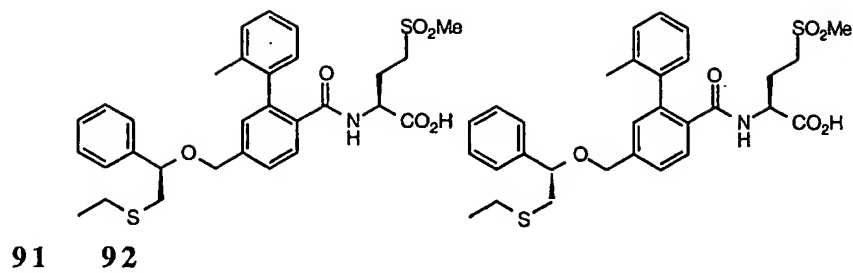
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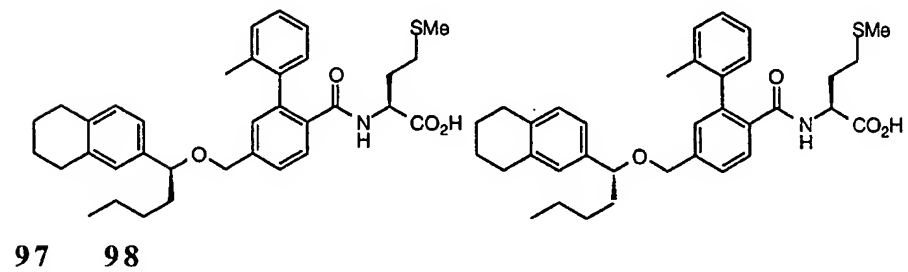
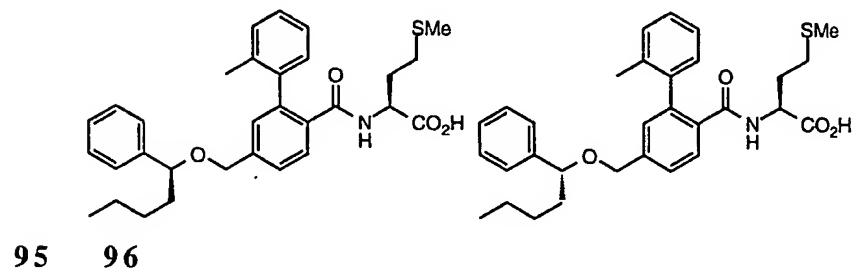


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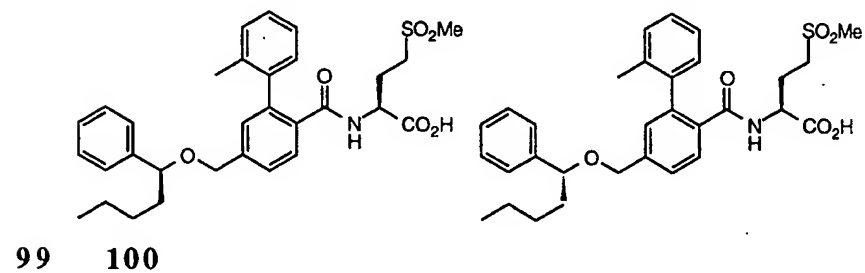
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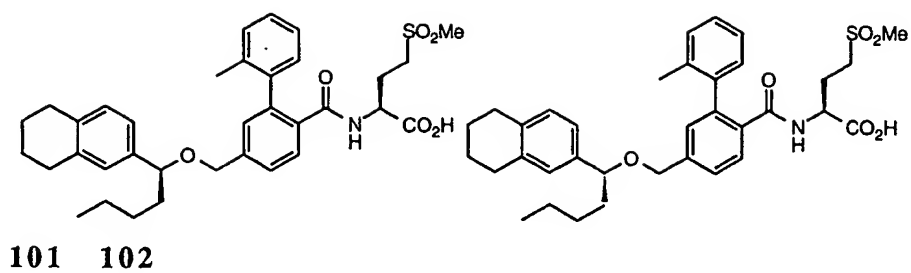
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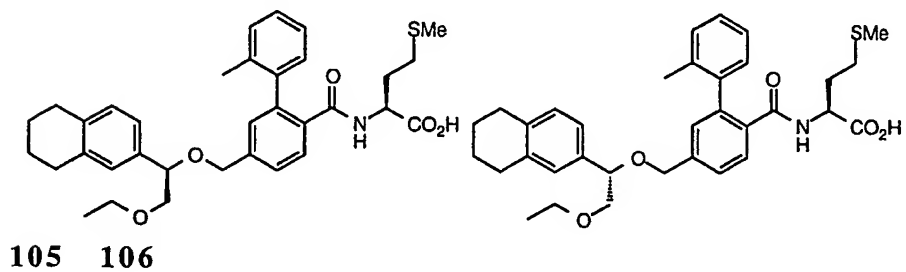
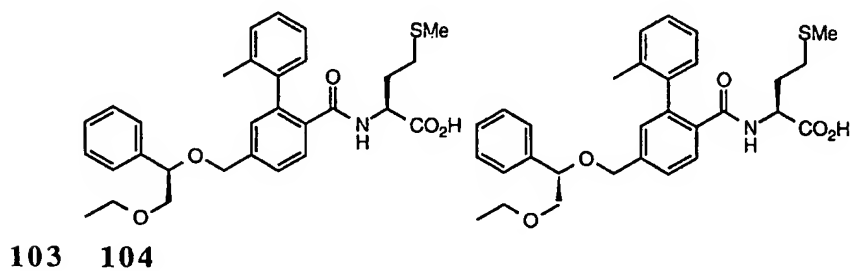
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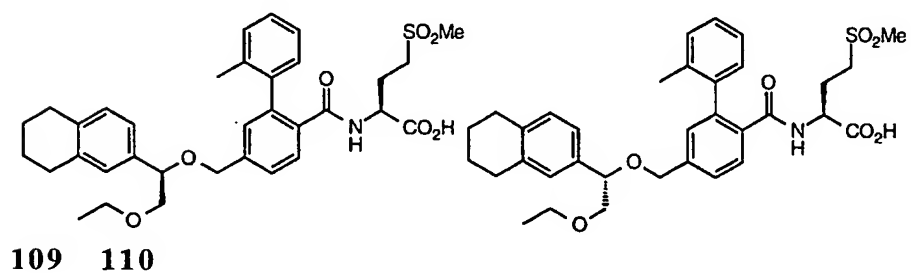
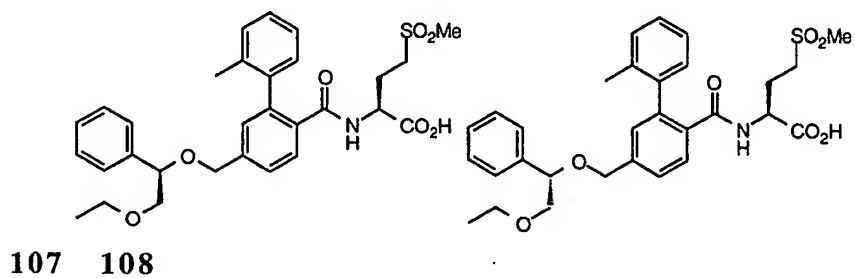
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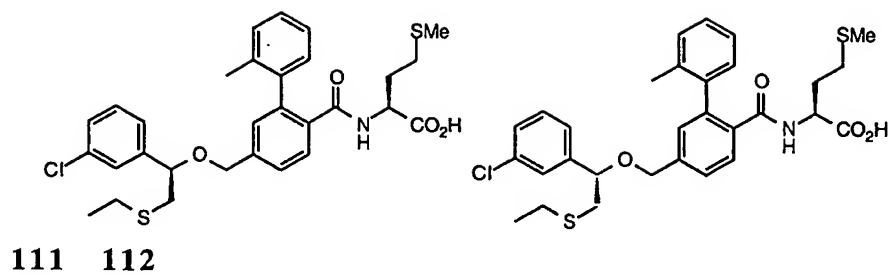
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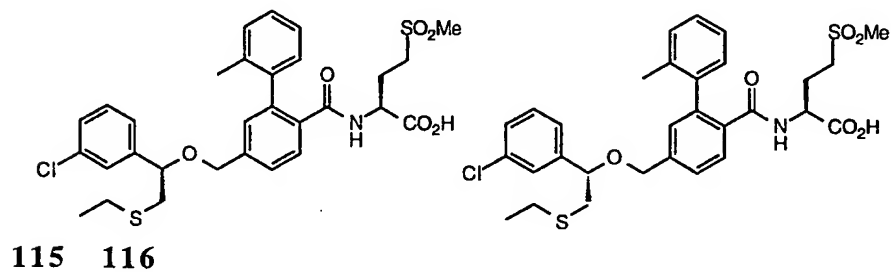
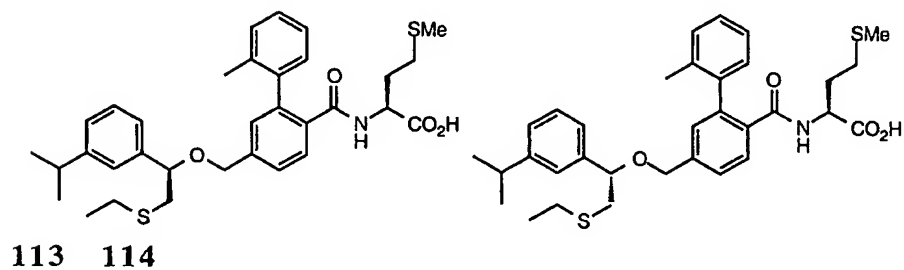
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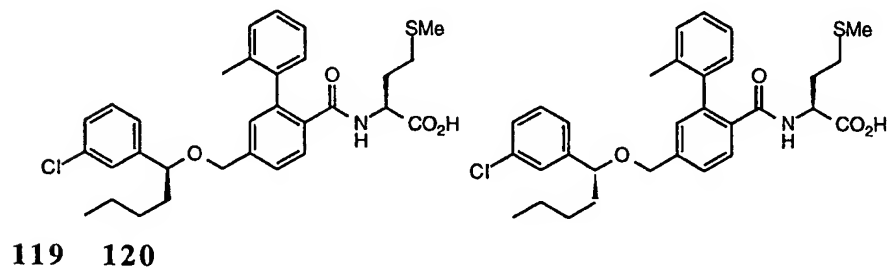
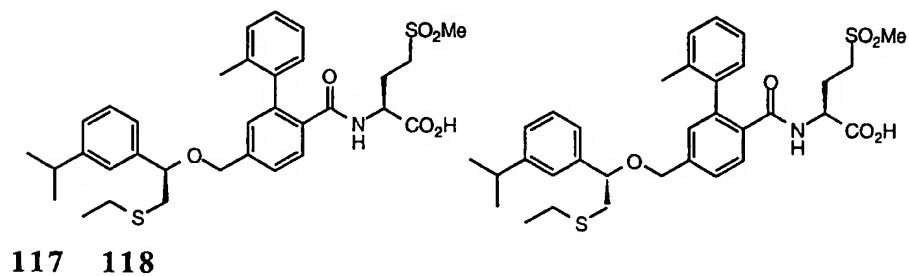
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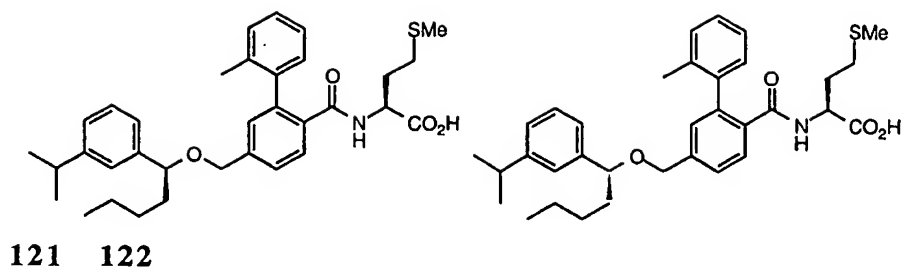
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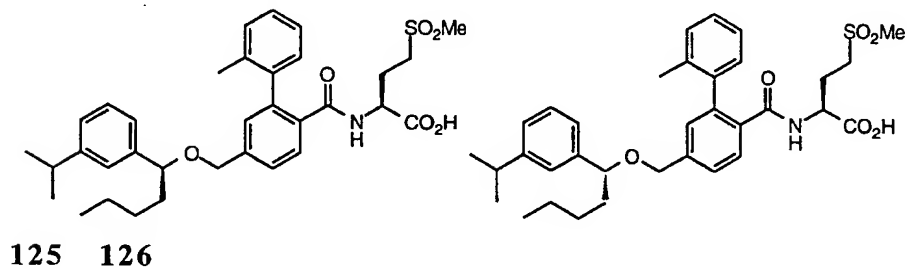
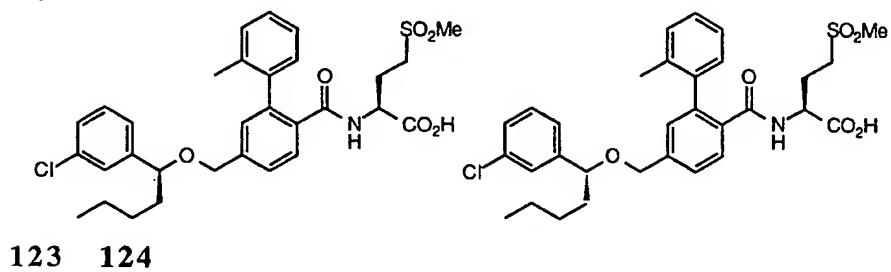
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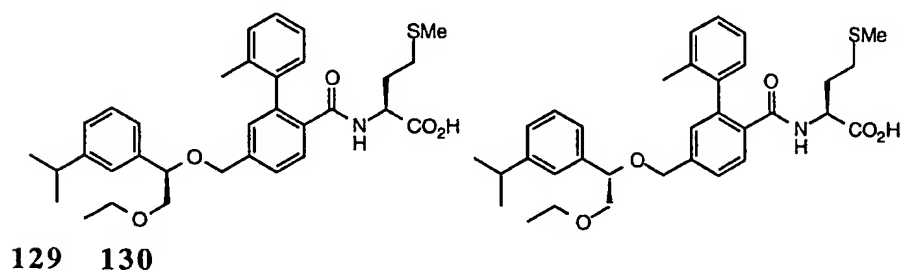
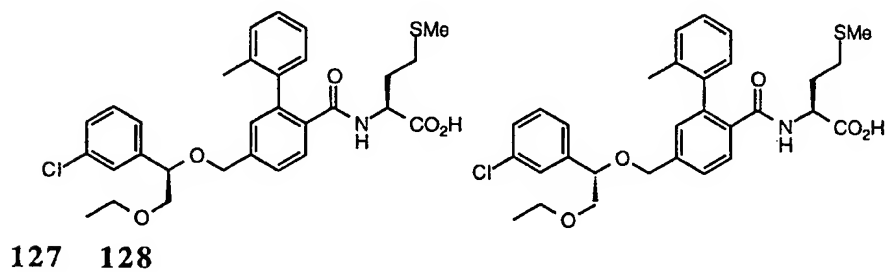
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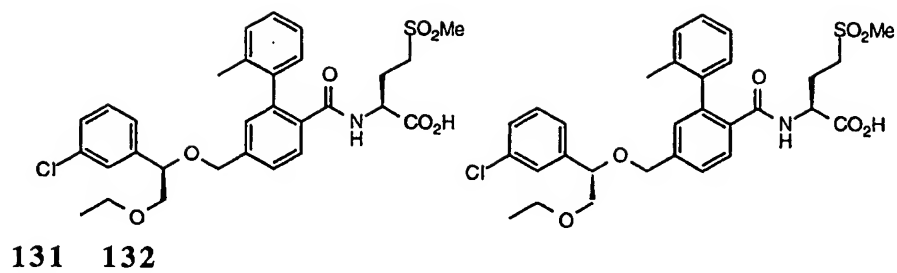
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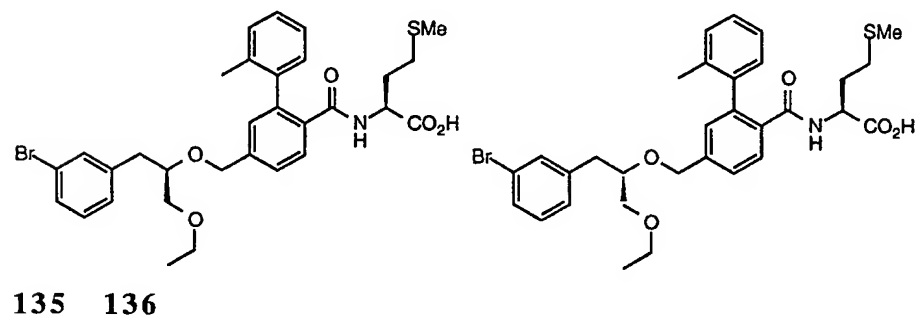
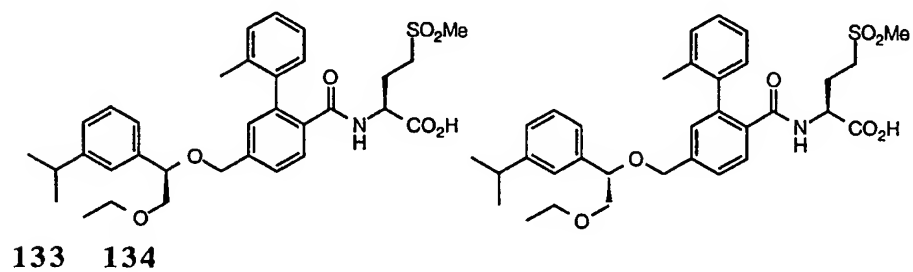
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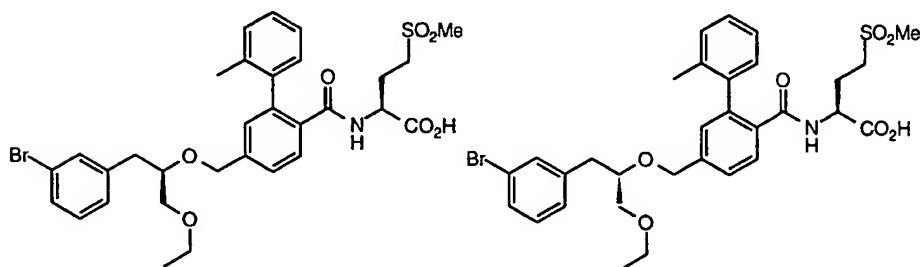
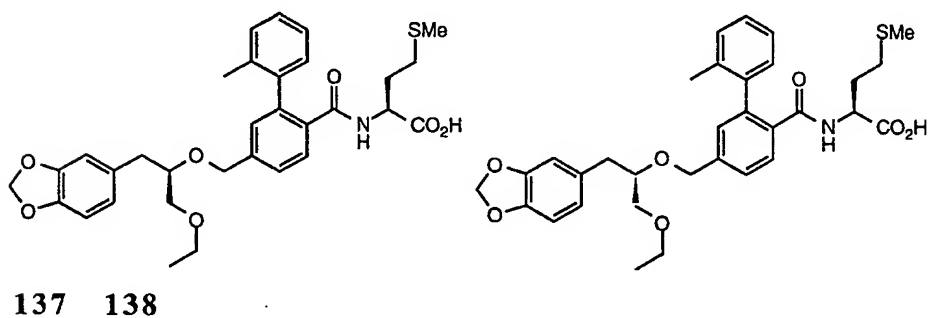
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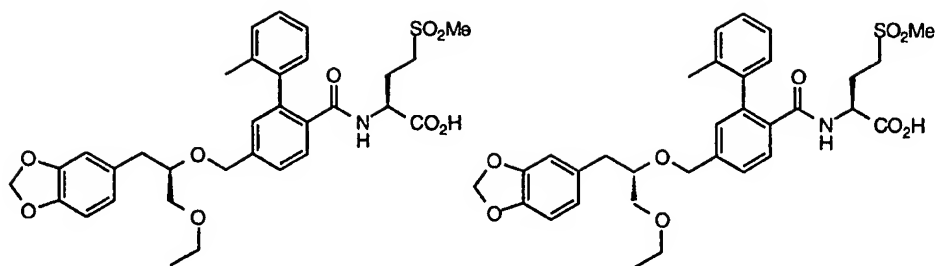
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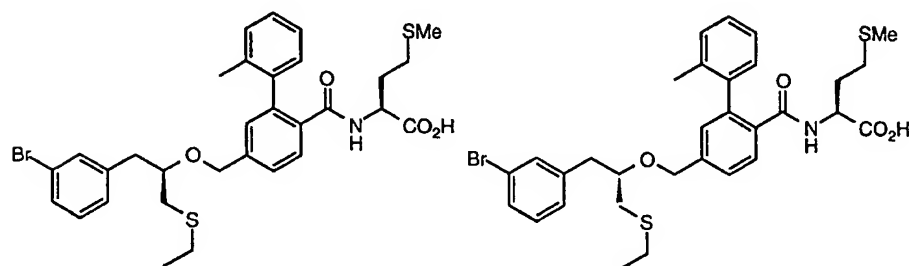


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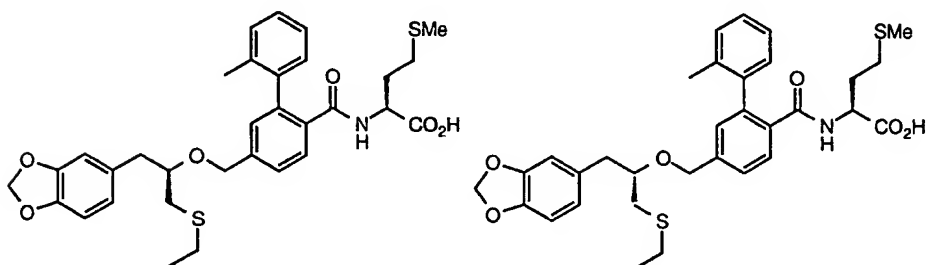


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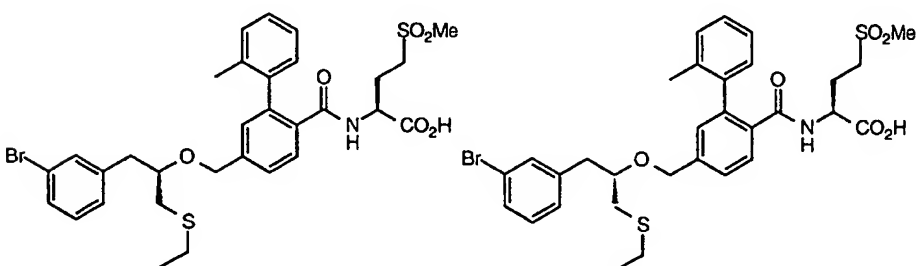


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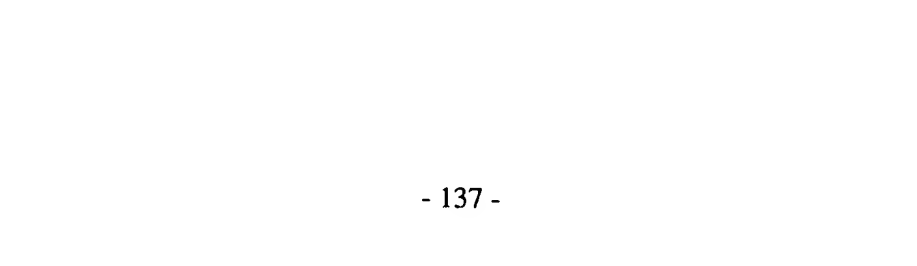
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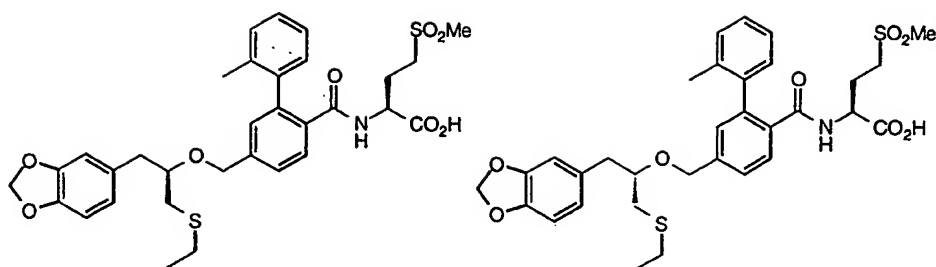
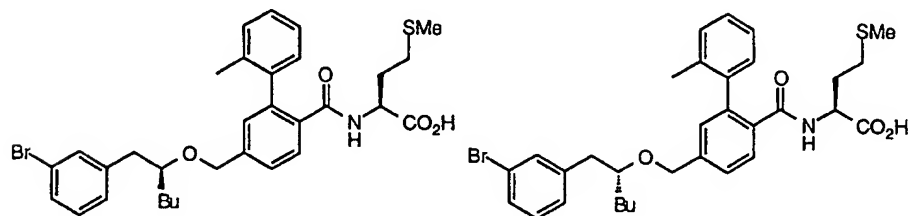
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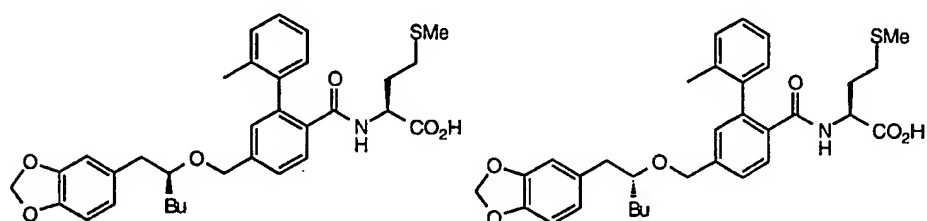
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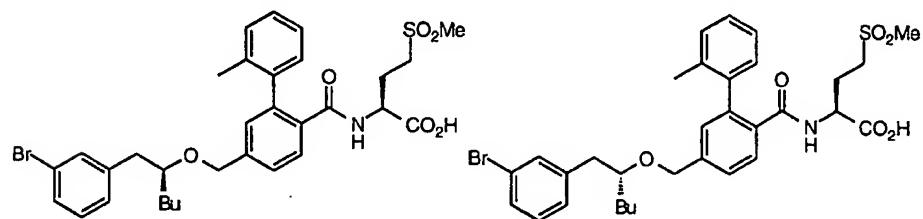
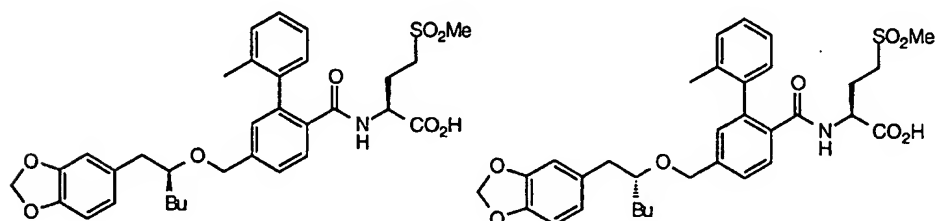


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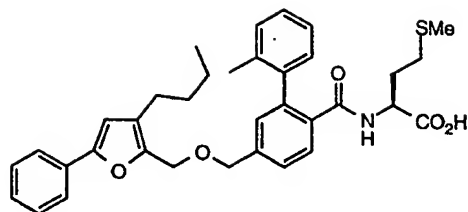
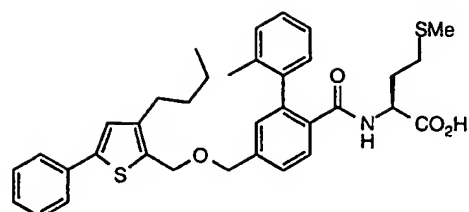
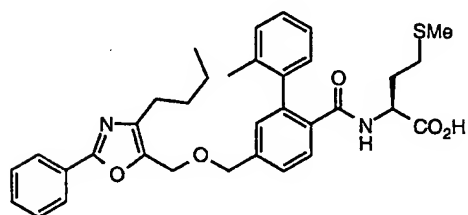
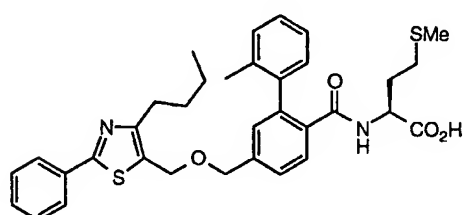
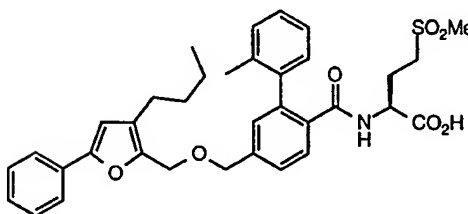
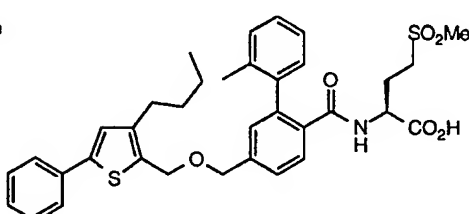
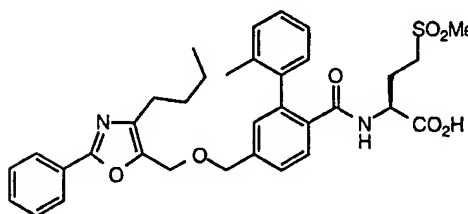
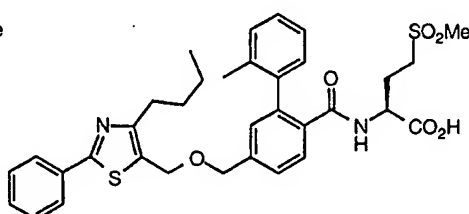
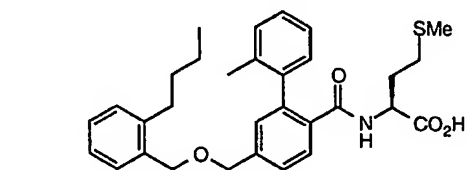
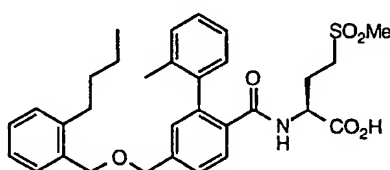
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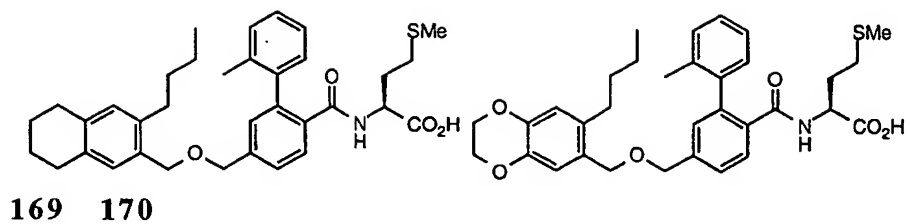
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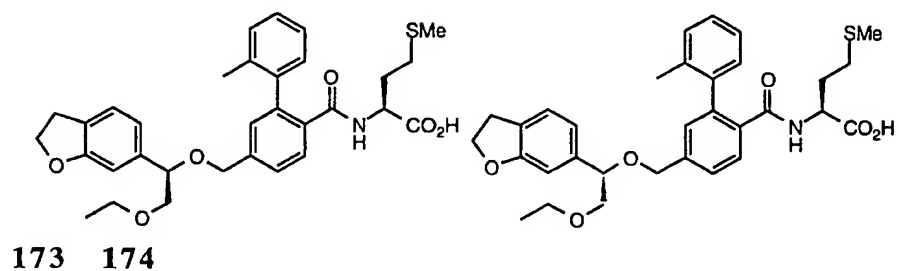
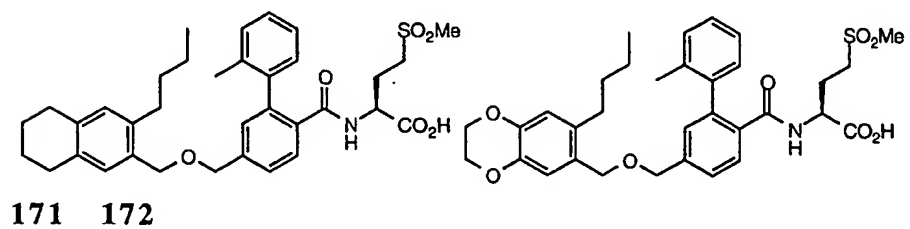
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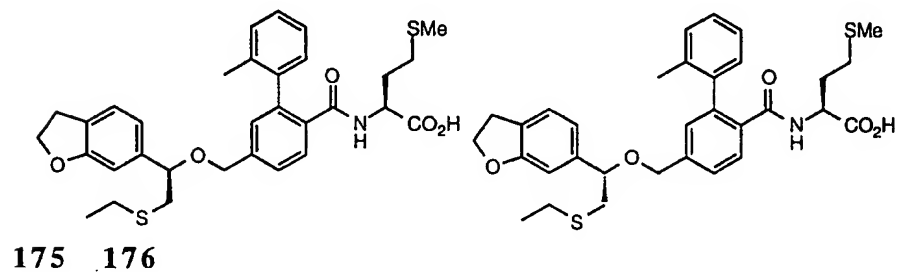
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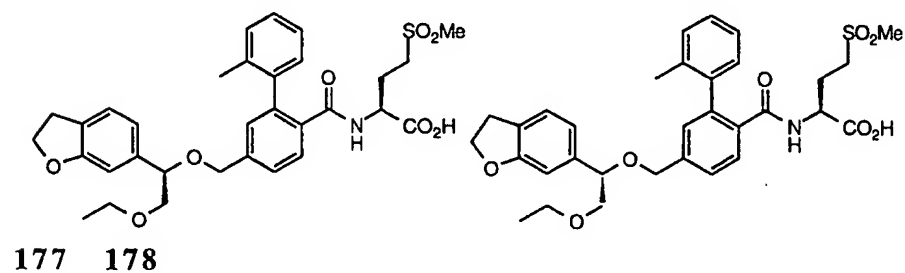
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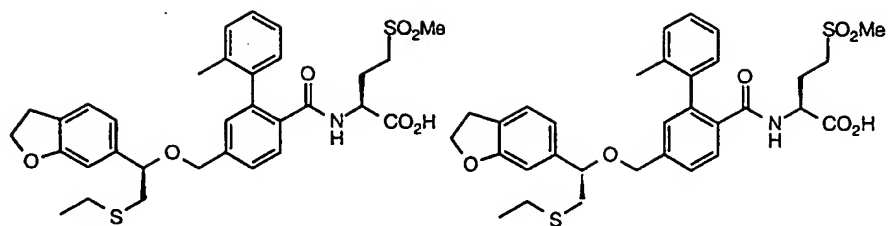


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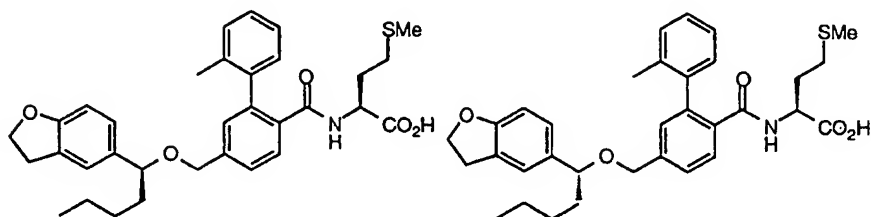


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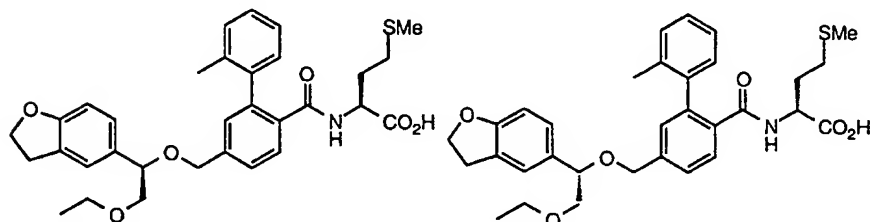




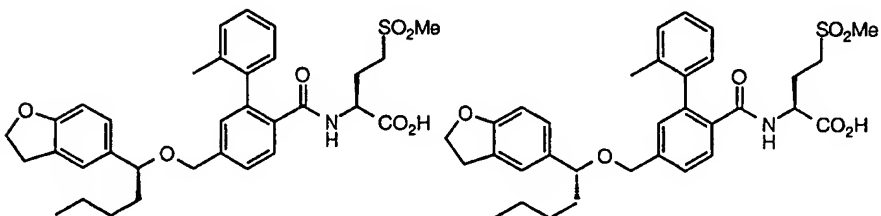
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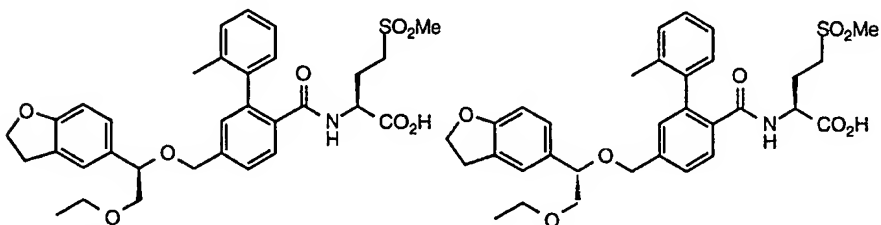
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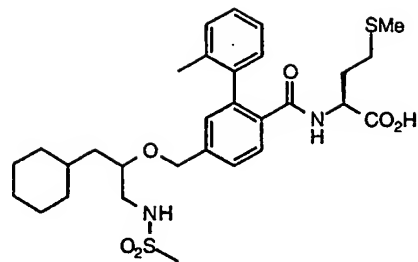
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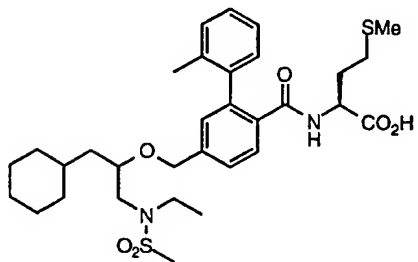
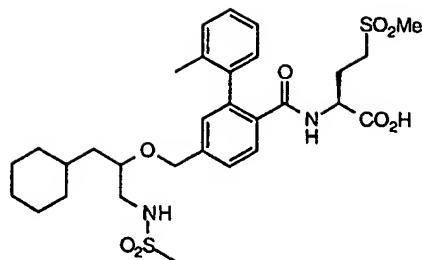
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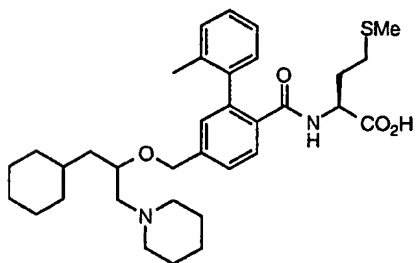
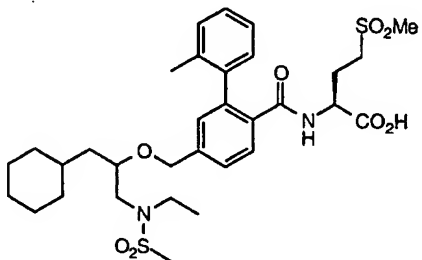


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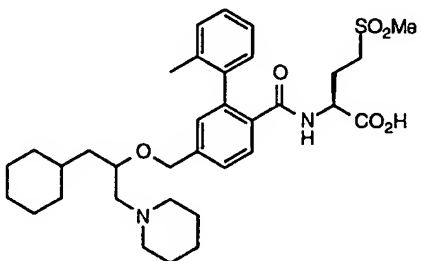


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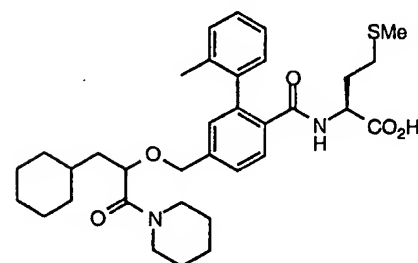
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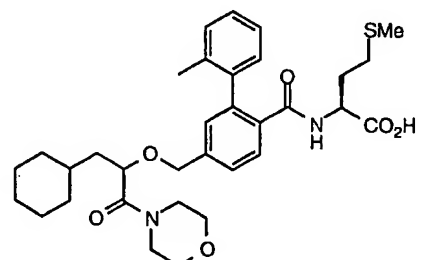
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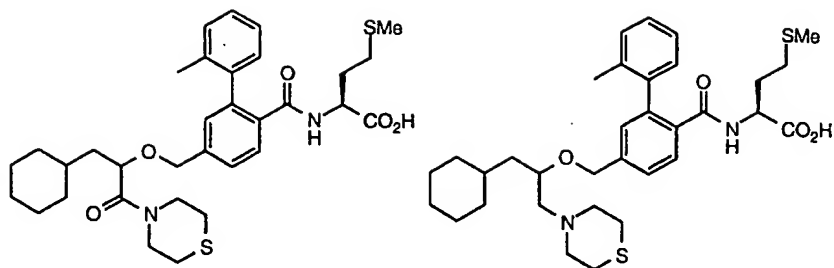


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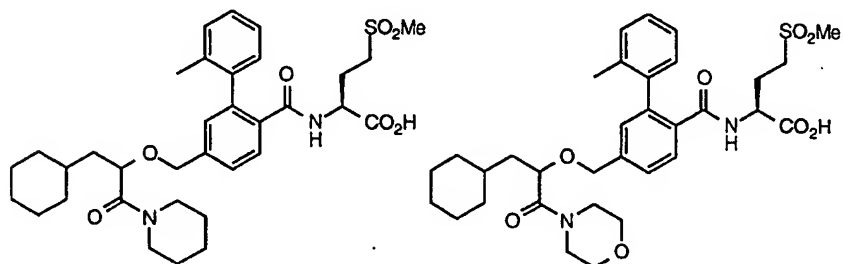
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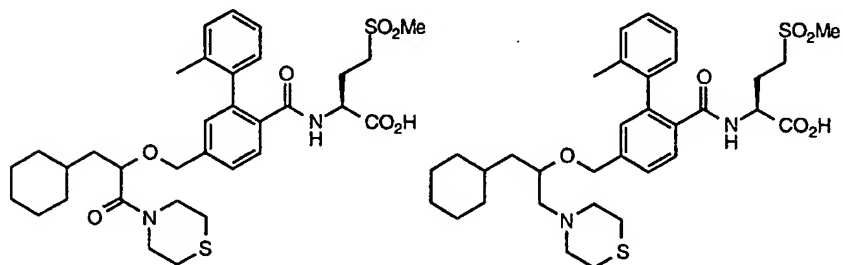


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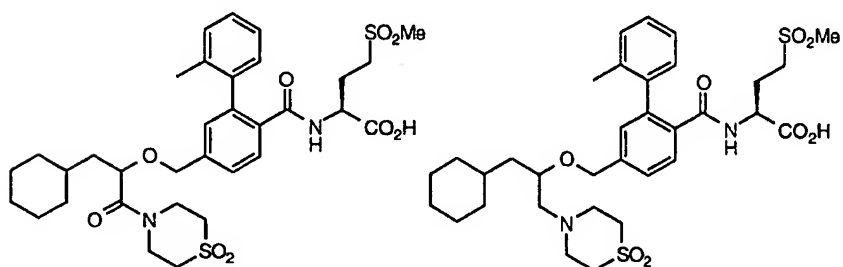


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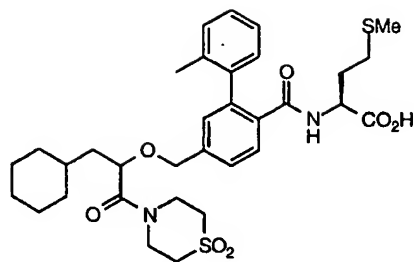
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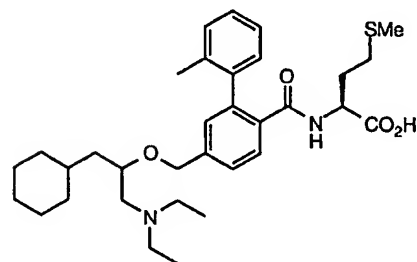
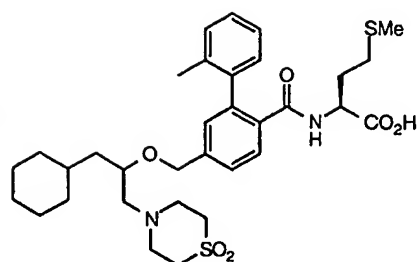


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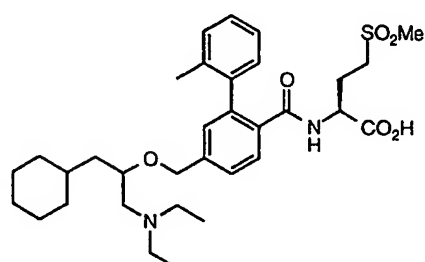
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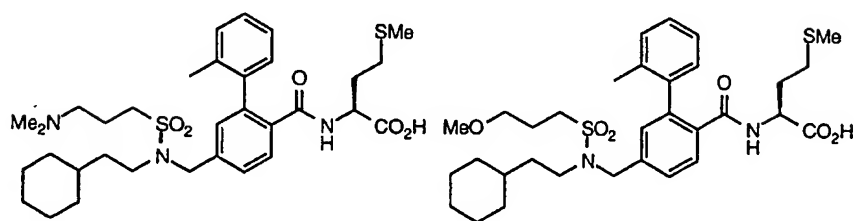
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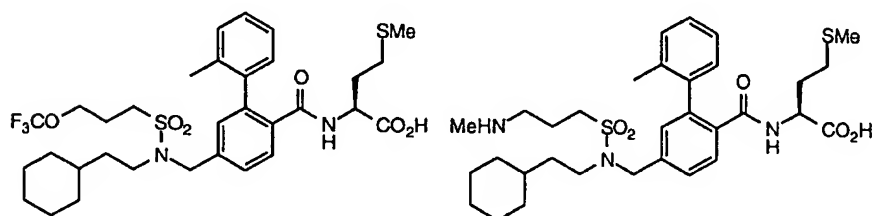


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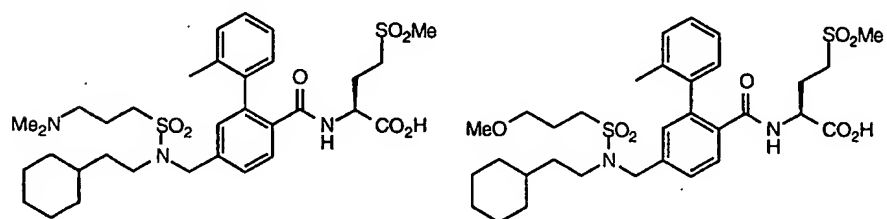
Table 8. Sulfonamides of the Type $ASO_2(B)N-L_1$ 

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1 2

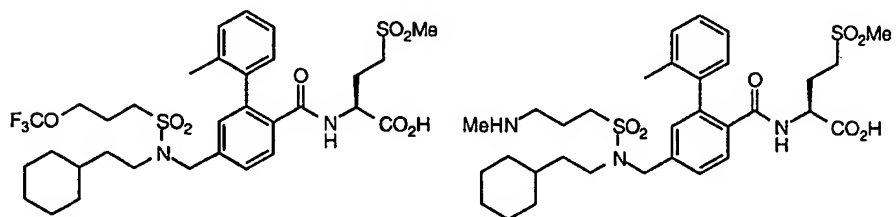


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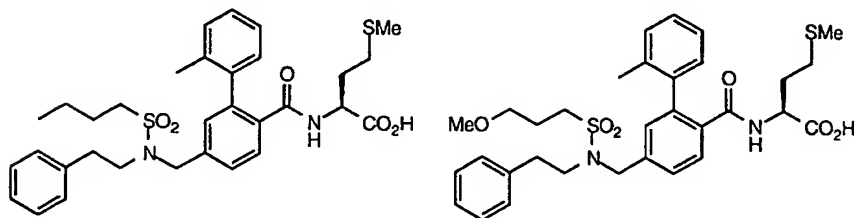
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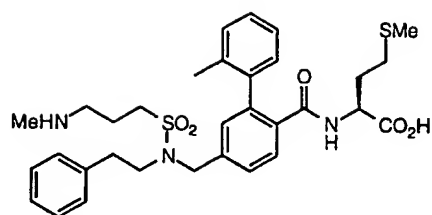
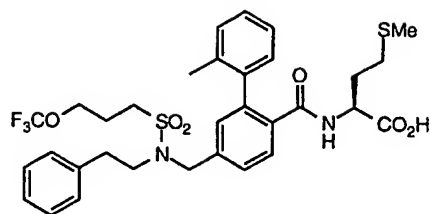


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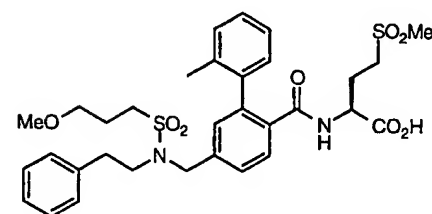
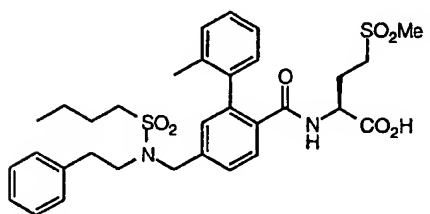


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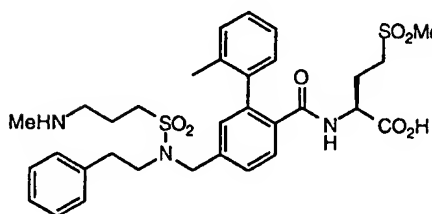
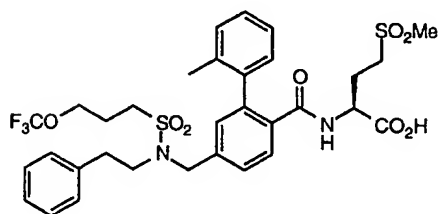


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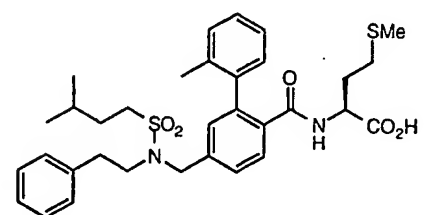
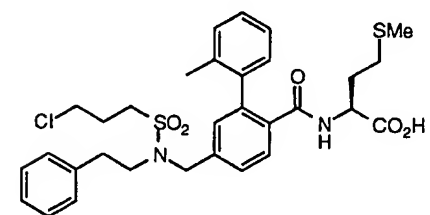


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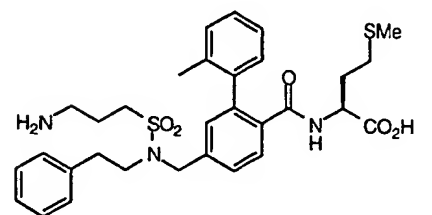
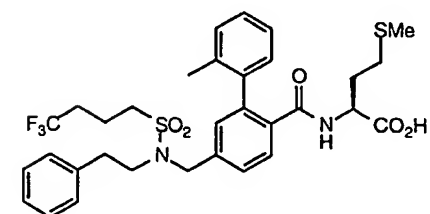
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15 16

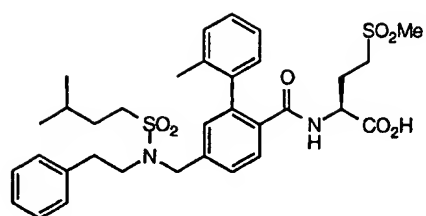
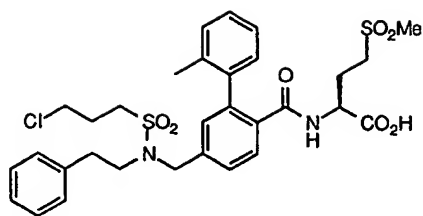


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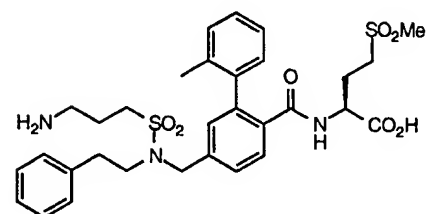
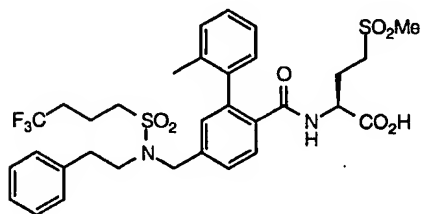


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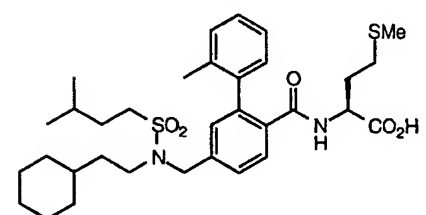
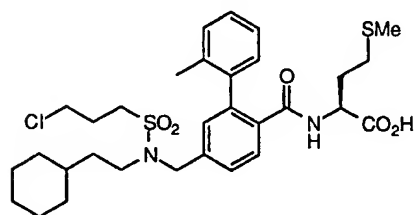


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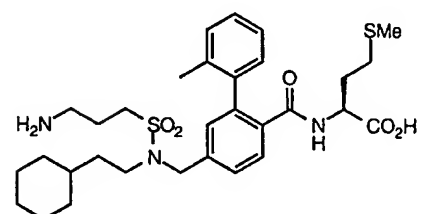
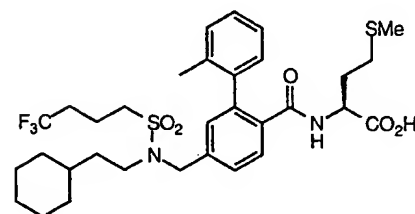


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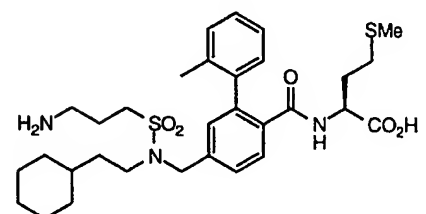
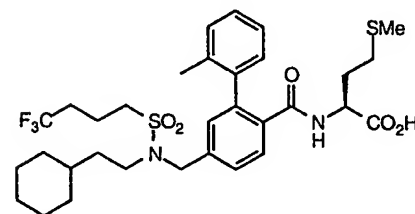
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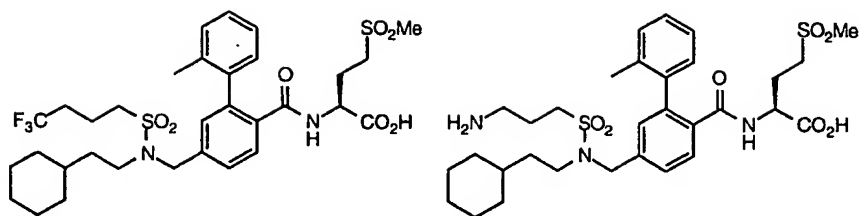


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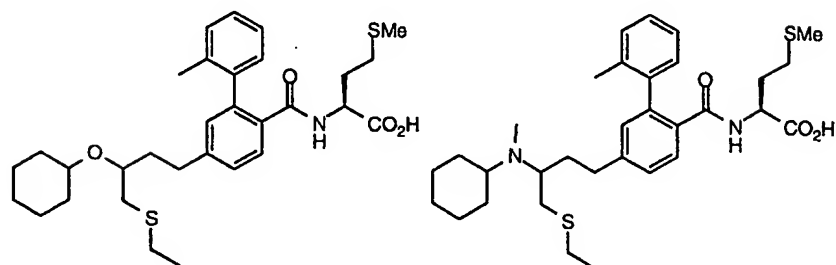


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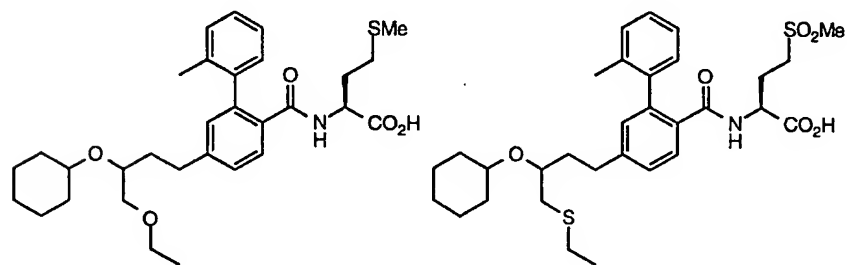
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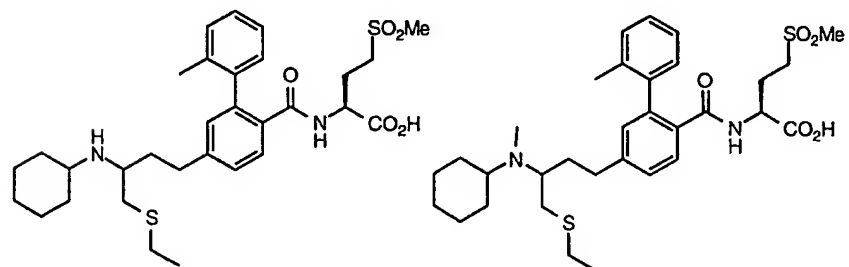
Table 9. Hydrocarbons of the Type A(B)CH₂-L₁

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1 2

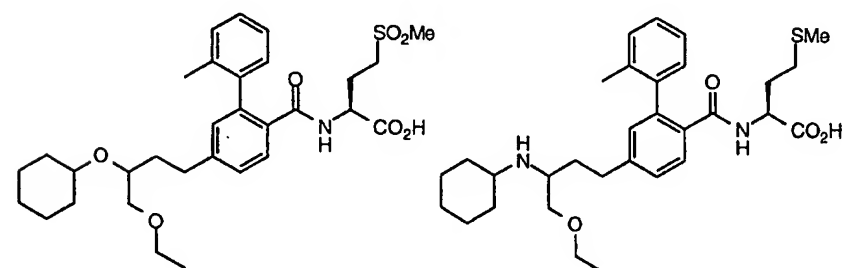


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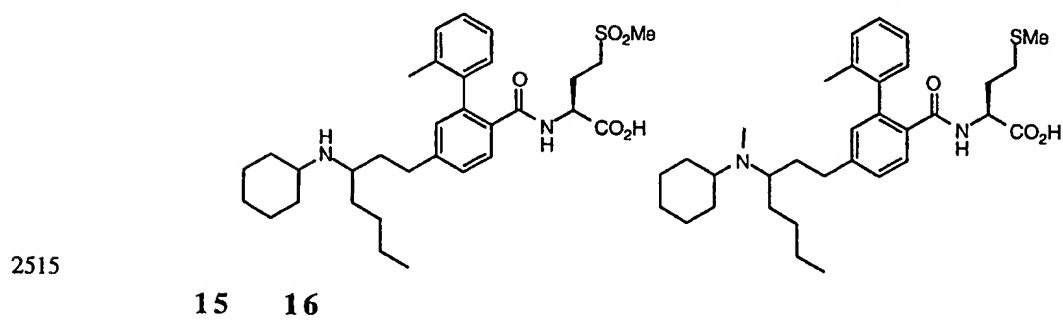
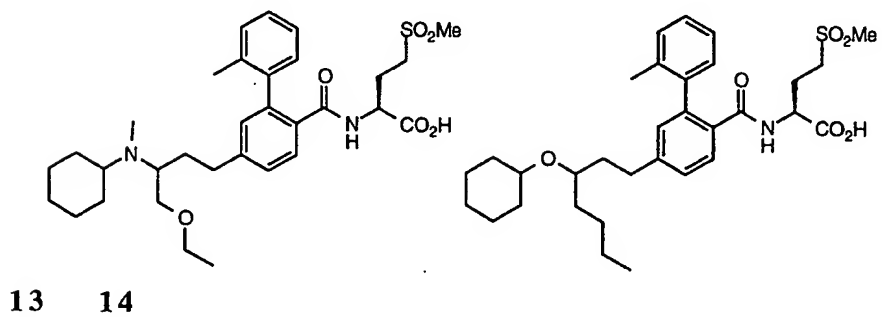
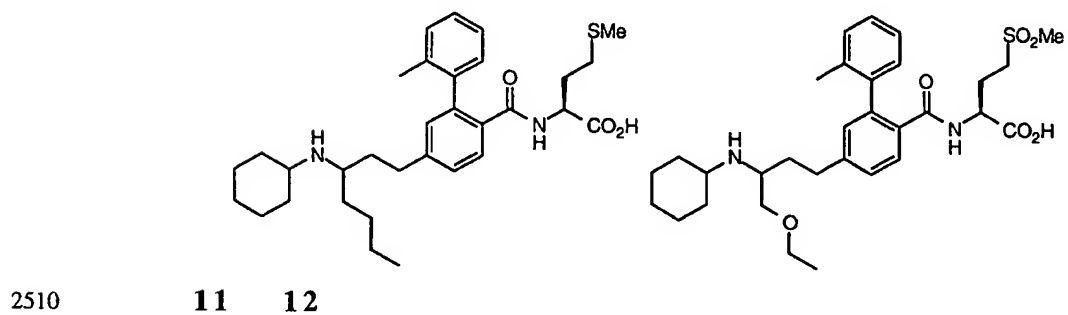
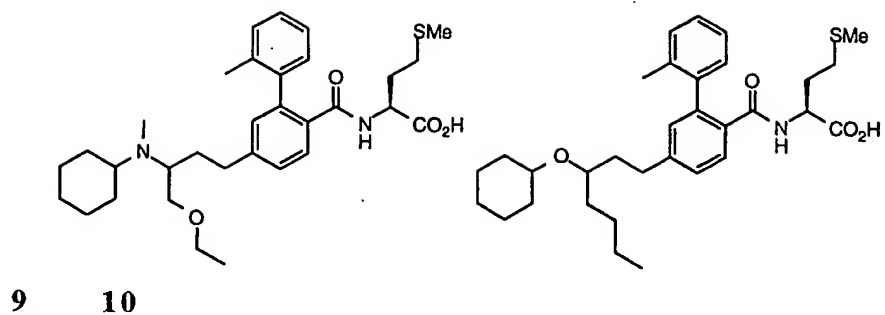
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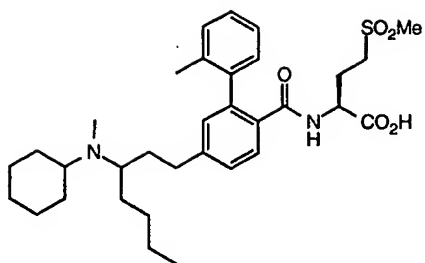
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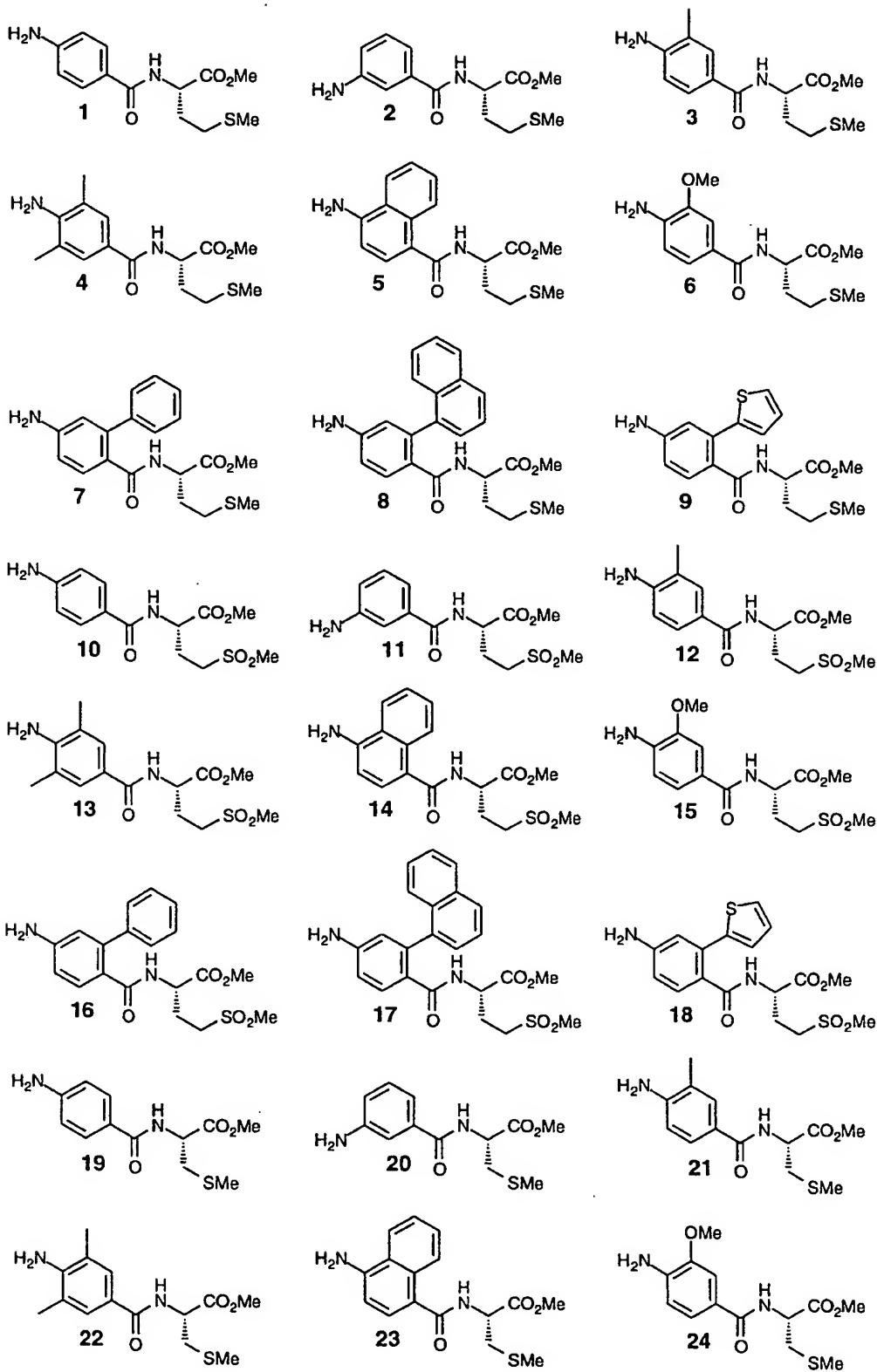
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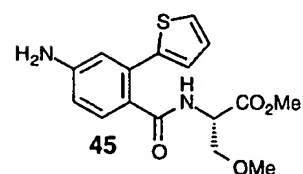
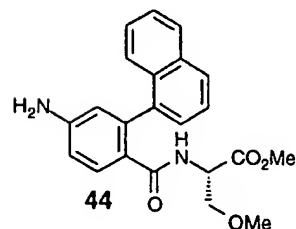
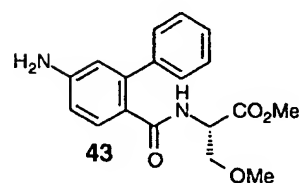
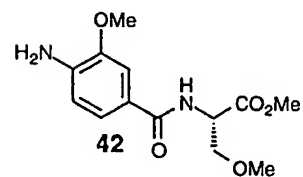
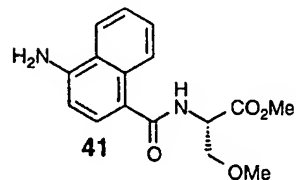
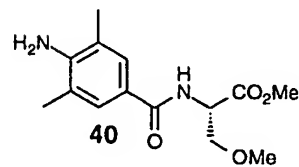
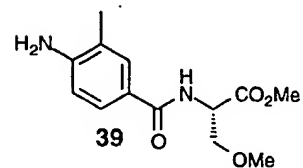
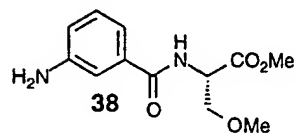
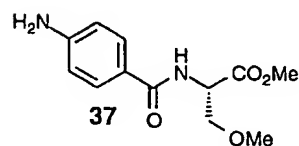
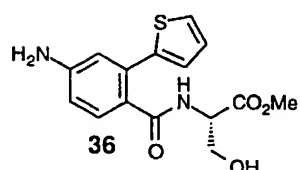
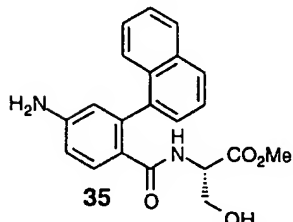
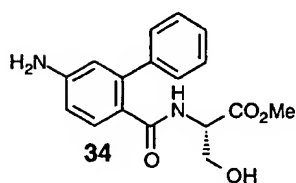
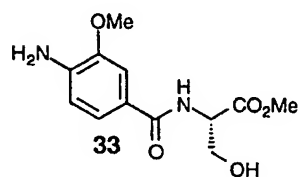
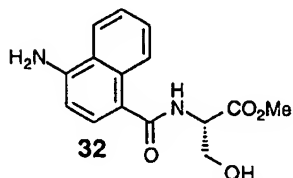
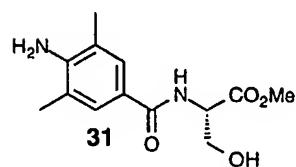
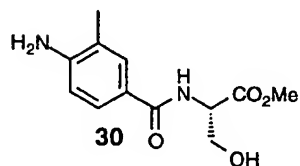
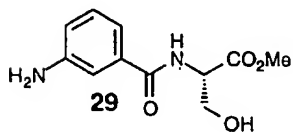
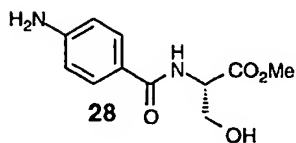
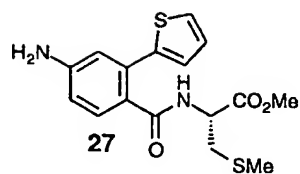
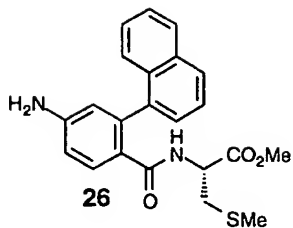
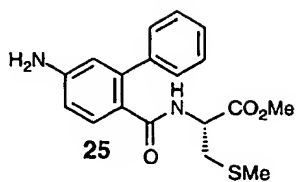


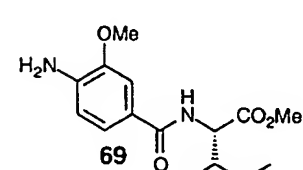
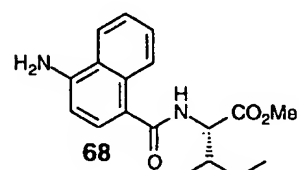
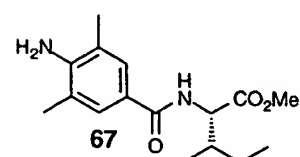
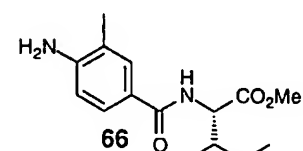
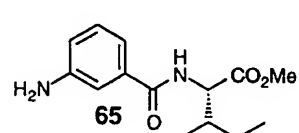
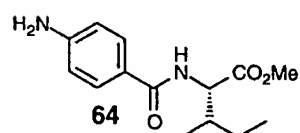
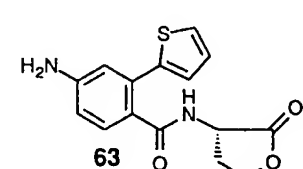
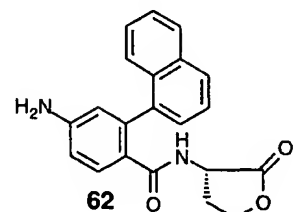
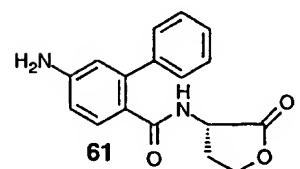
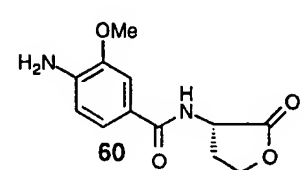
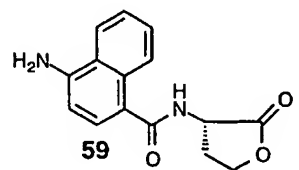
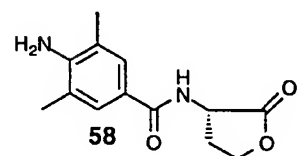
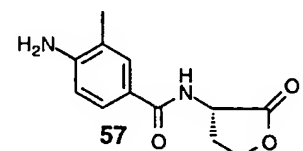
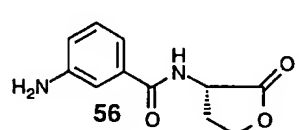
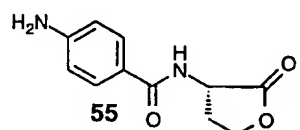
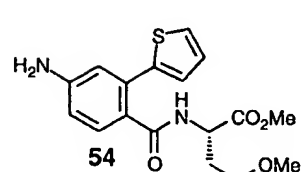
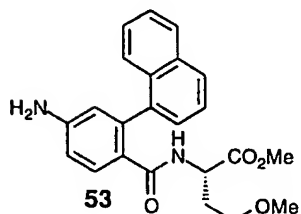
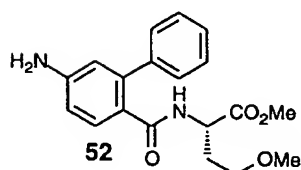
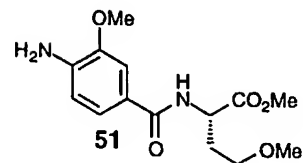
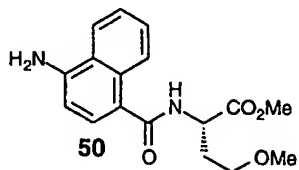
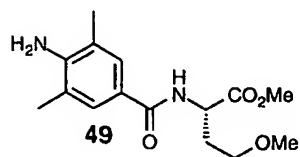
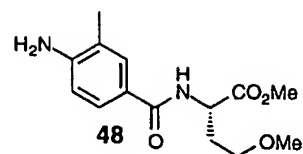
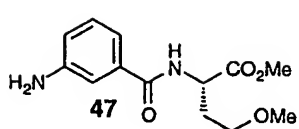
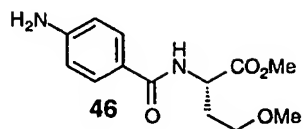


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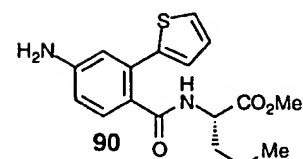
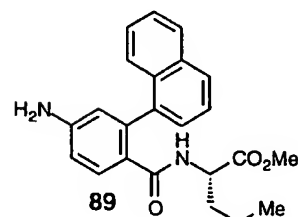
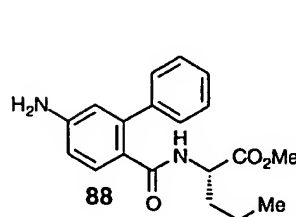
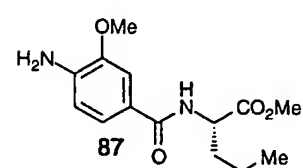
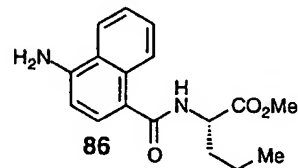
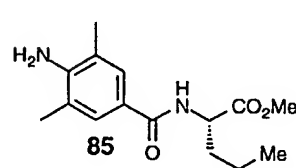
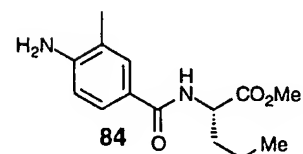
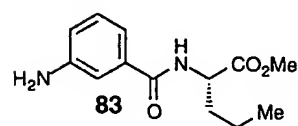
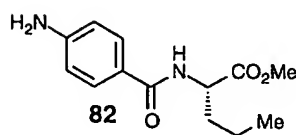
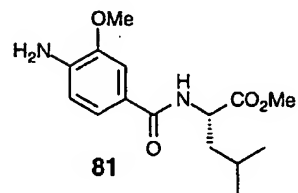
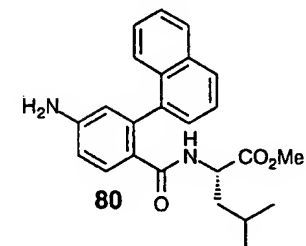
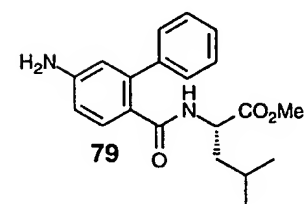
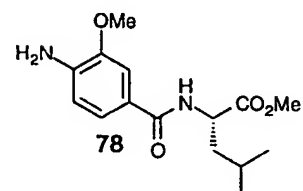
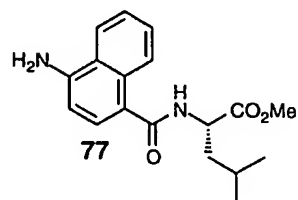
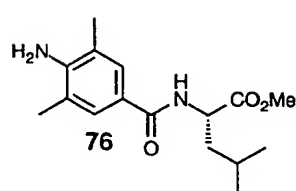
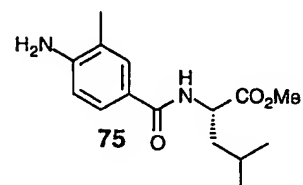
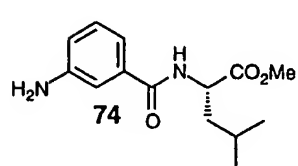
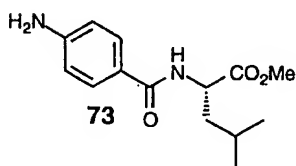
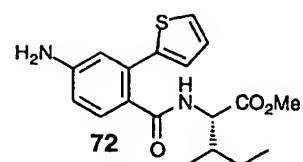
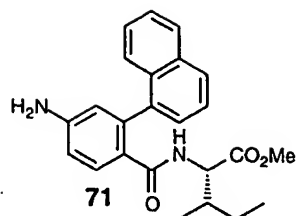
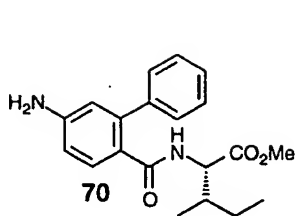
2520 Table 10. Amines of the type B-NH₂

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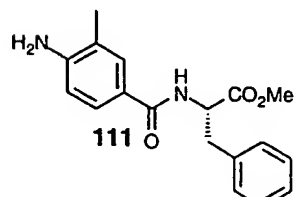
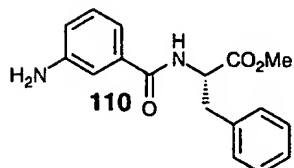
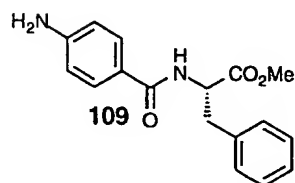
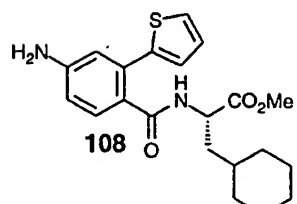
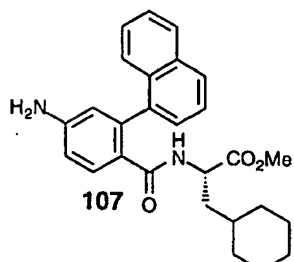
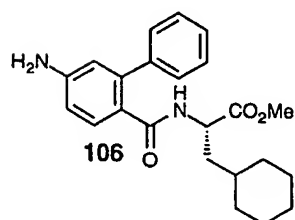
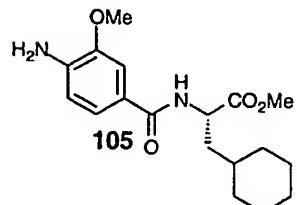
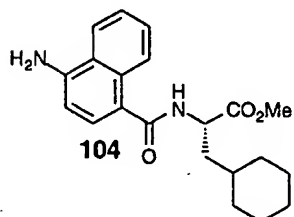
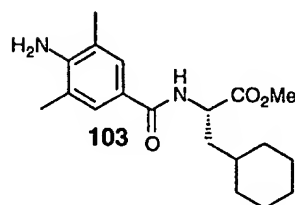
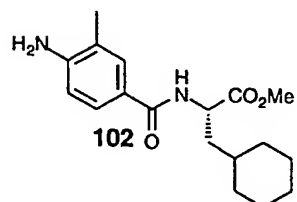
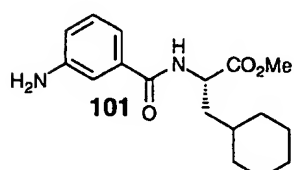
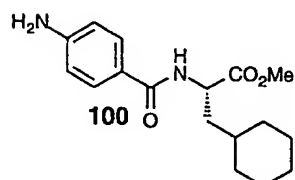
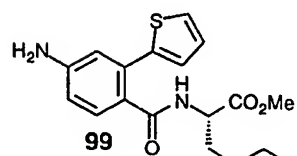
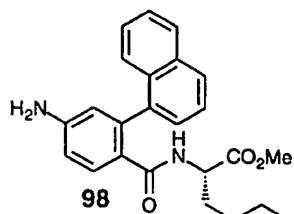
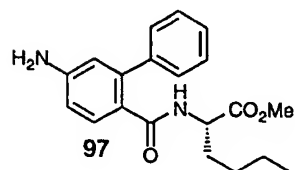
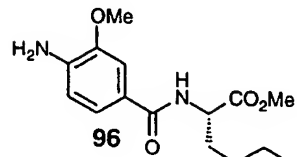
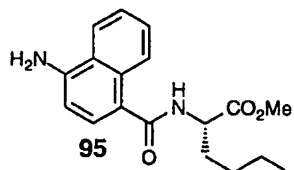
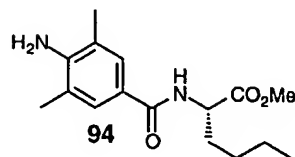
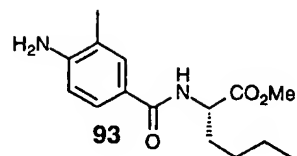
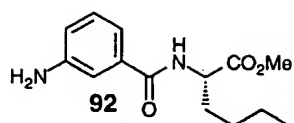
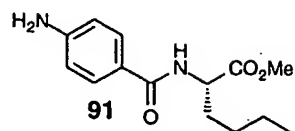


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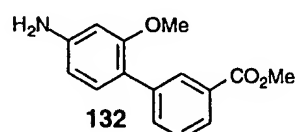
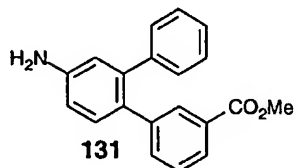
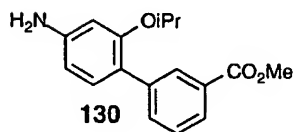
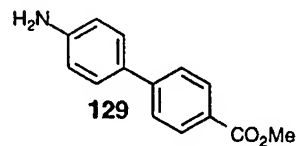
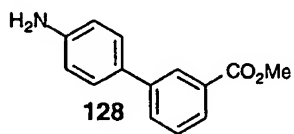
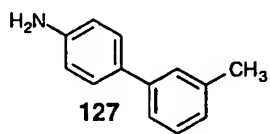
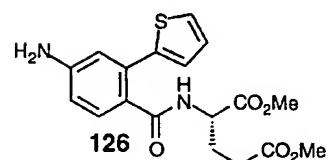
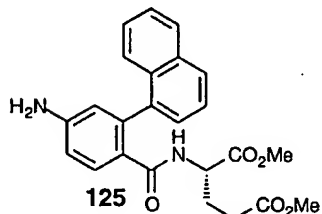
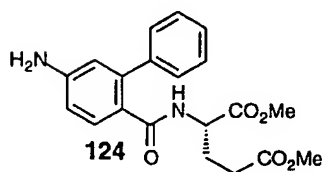
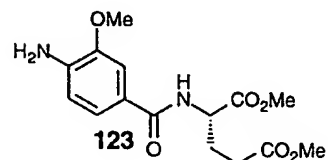
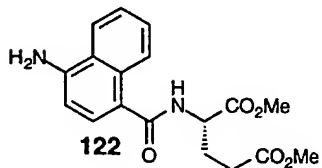
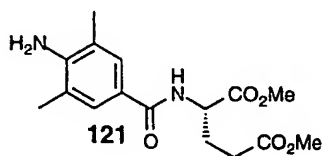
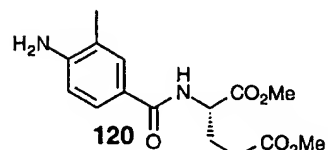
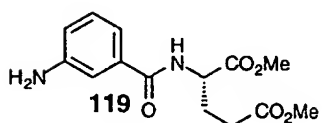
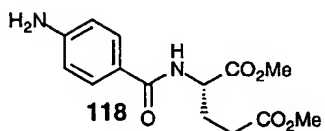
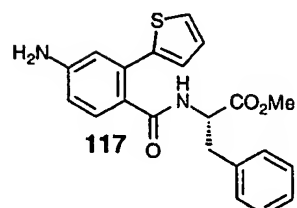
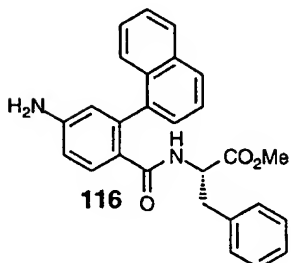
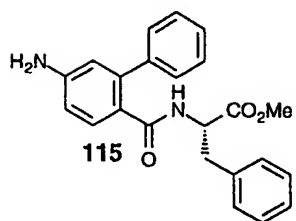
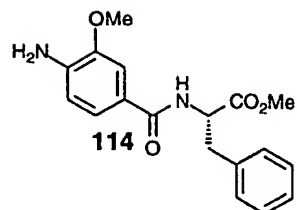
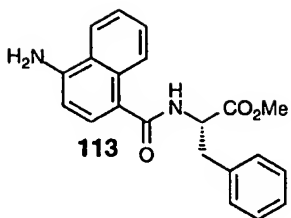
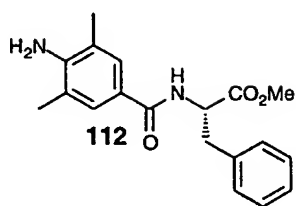


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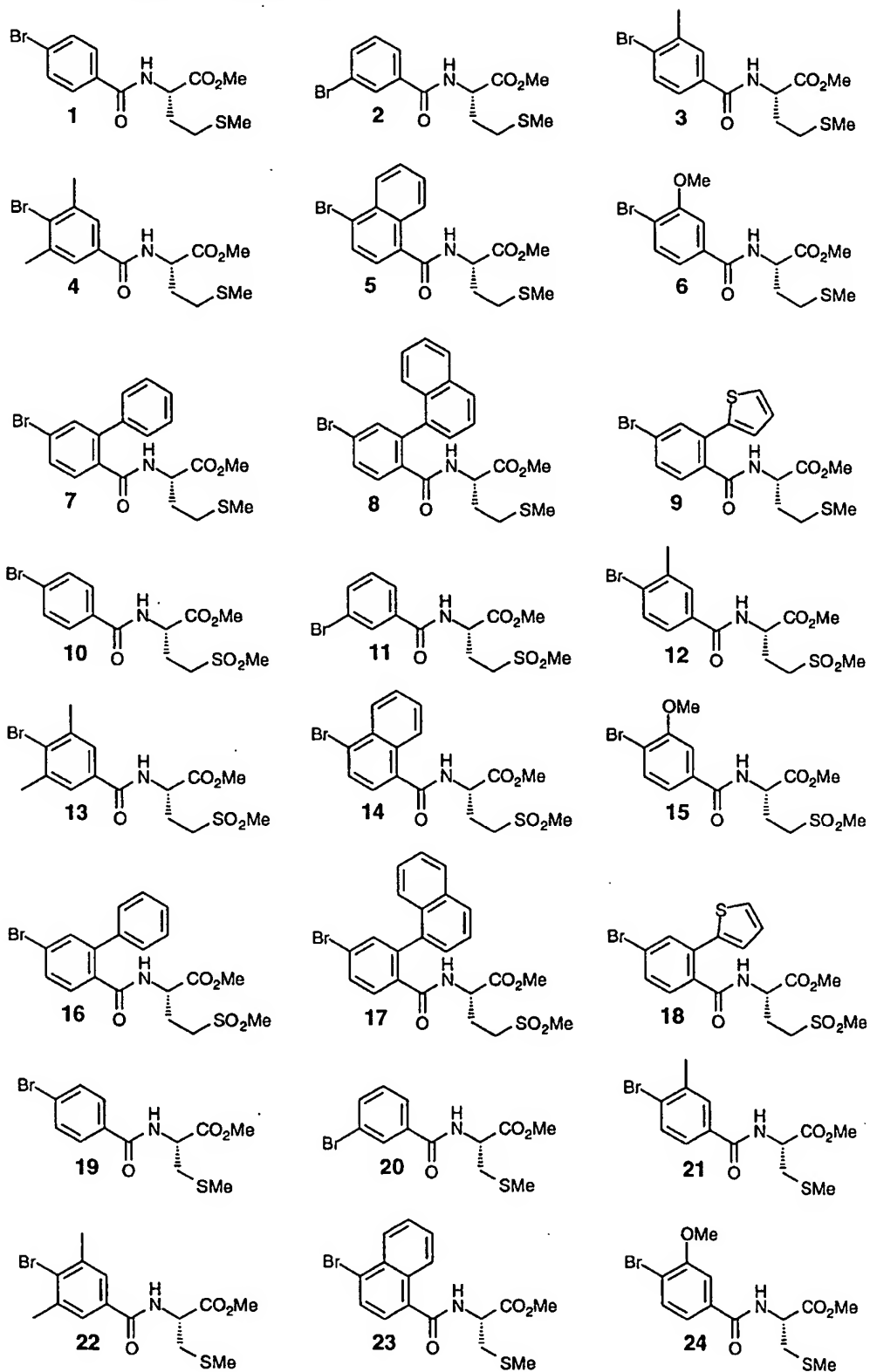
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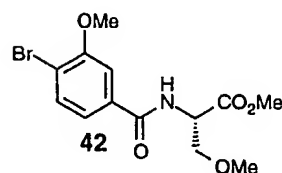
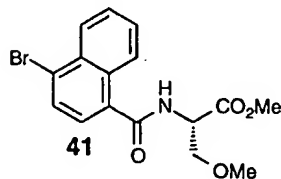
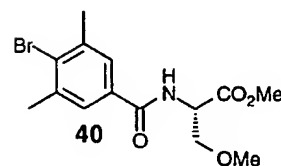
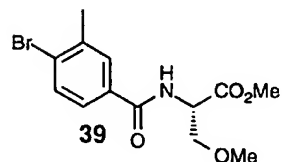
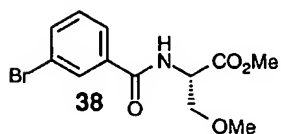
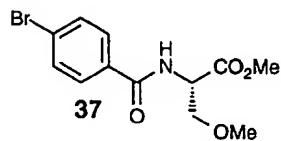
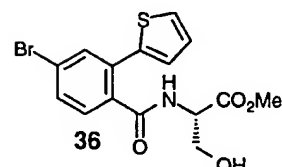
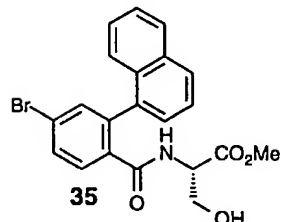
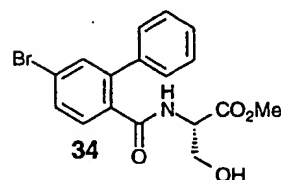
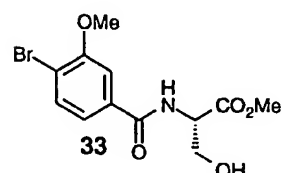
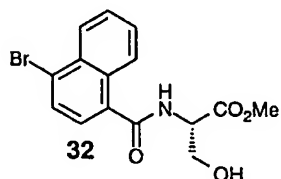
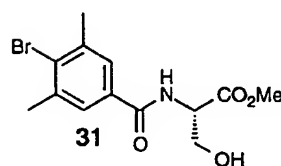
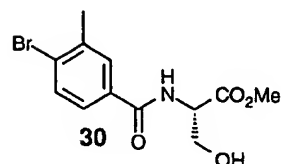
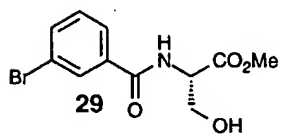
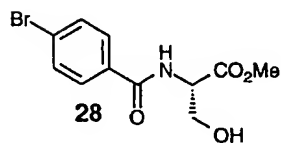
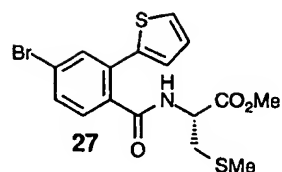
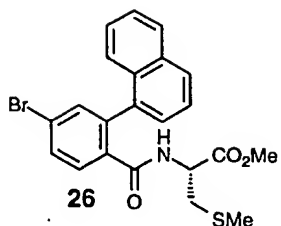
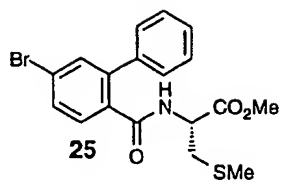
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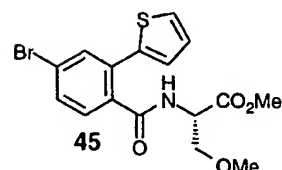
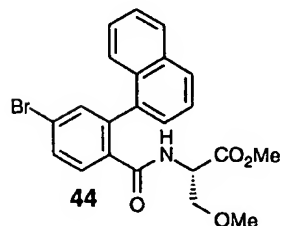
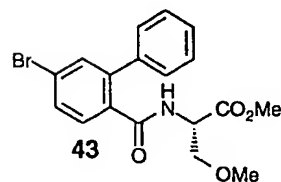
Table 11. Bromides of the type B-Br

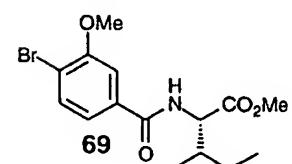
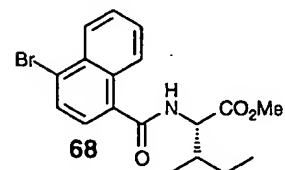
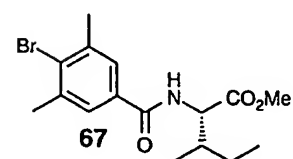
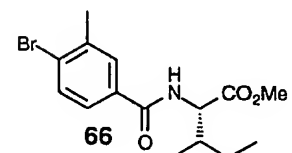
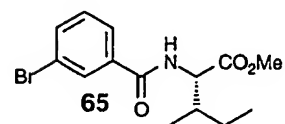
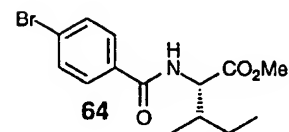
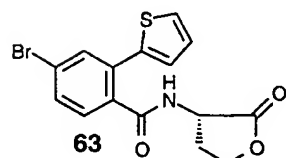
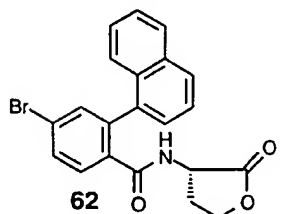
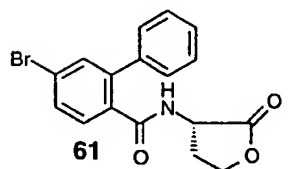
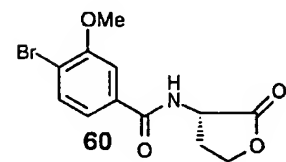
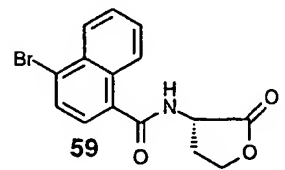
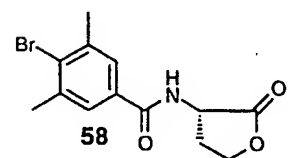
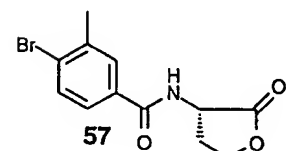
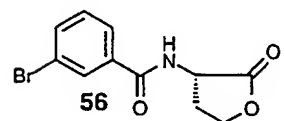
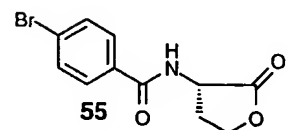
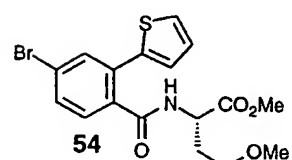
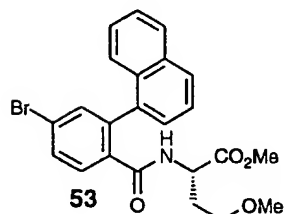
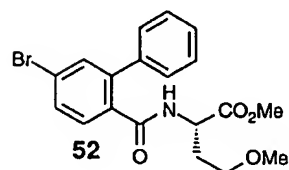
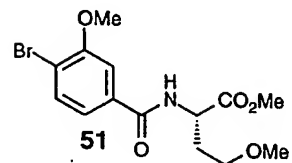
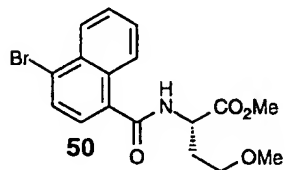
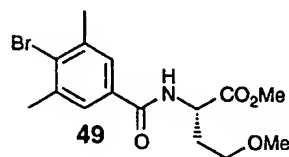
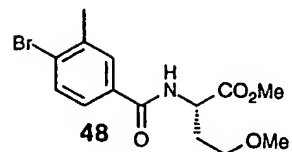
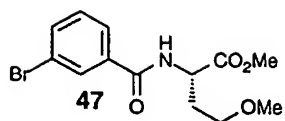
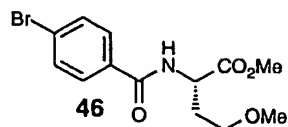


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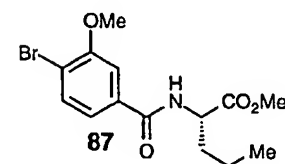
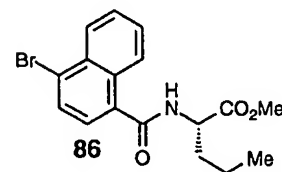
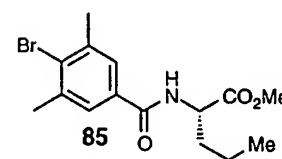
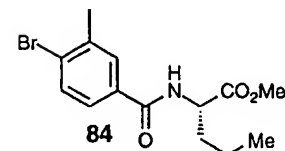
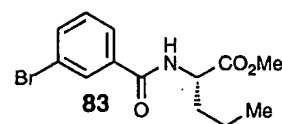
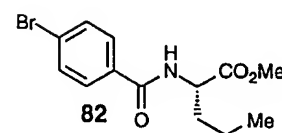
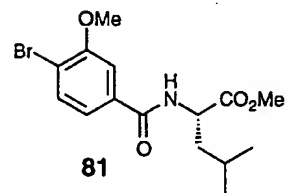
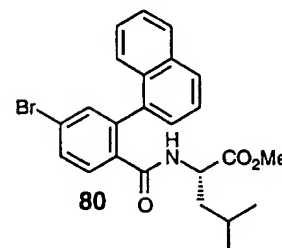
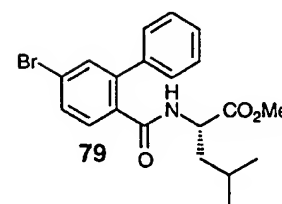
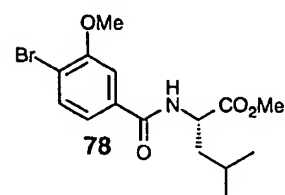
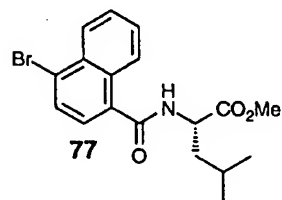
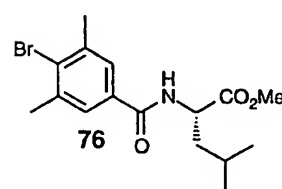
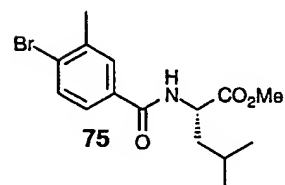
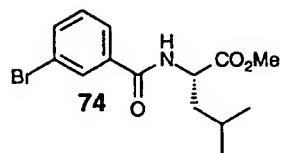
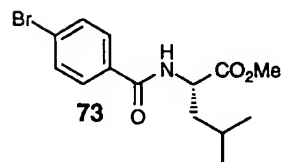
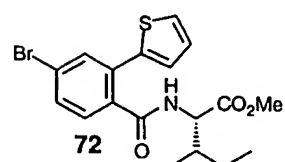
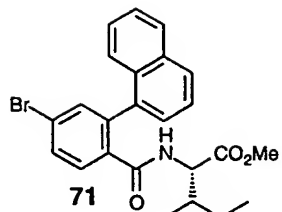
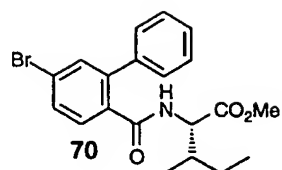
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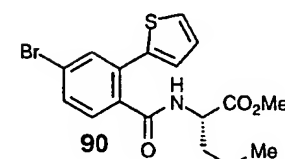
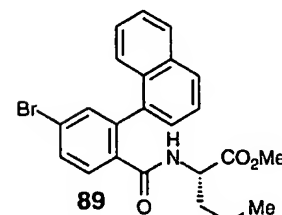
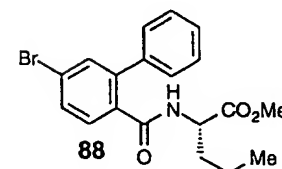


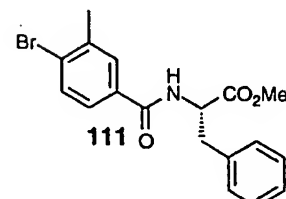
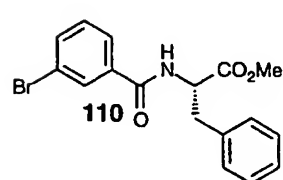
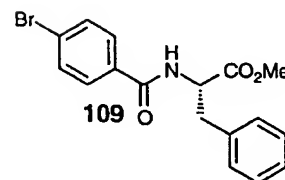
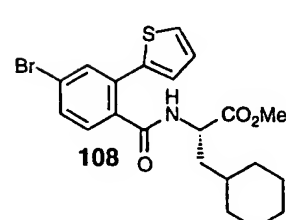
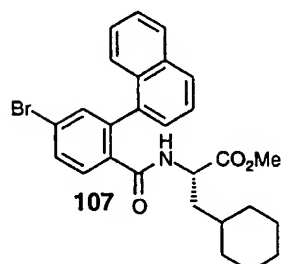
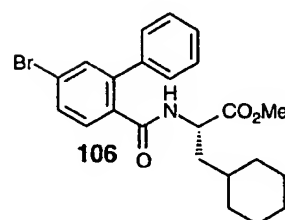
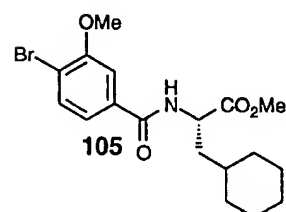
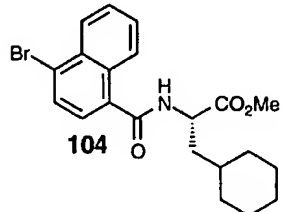
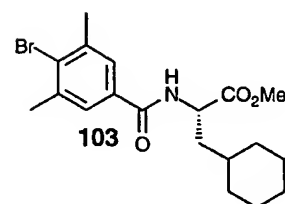
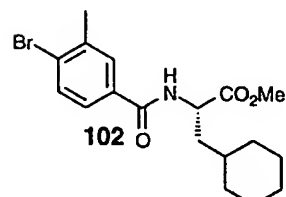
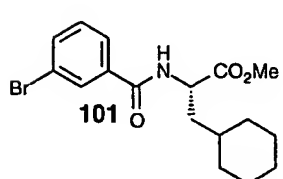
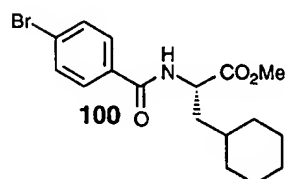
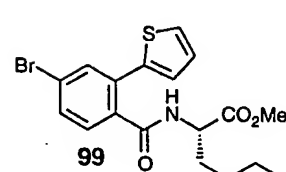
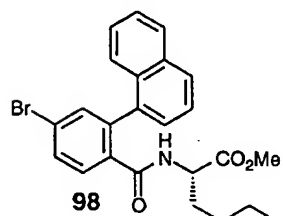
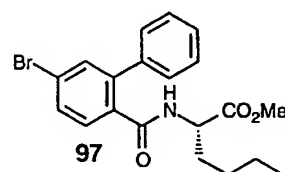
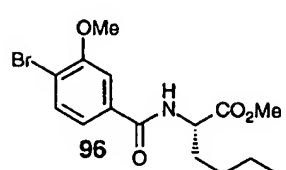
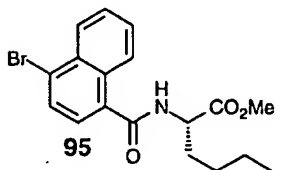
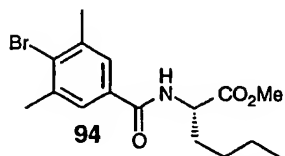
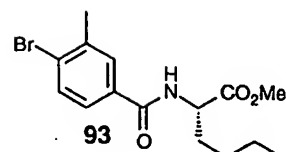
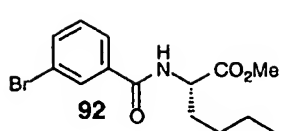
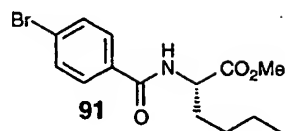
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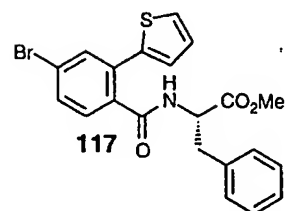
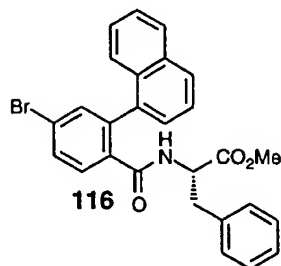
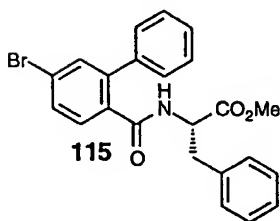
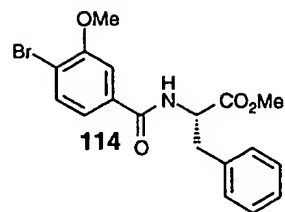
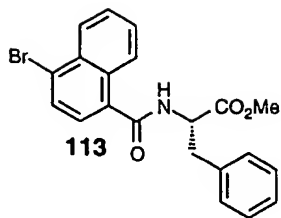
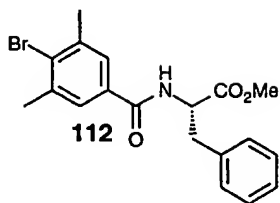


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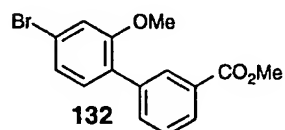
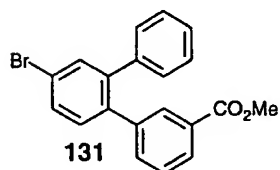
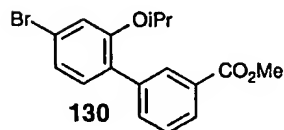
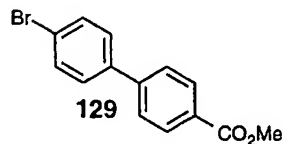
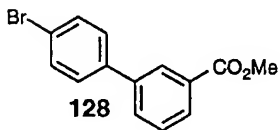
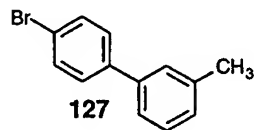
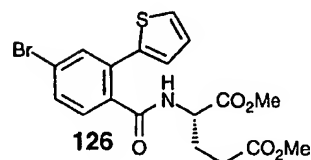
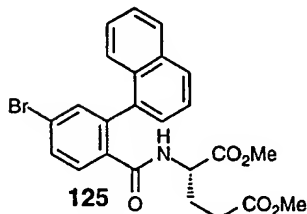
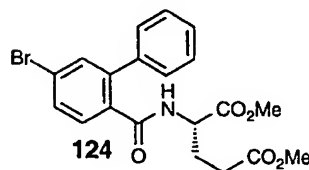
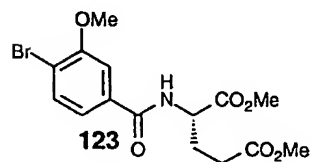
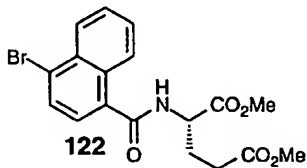
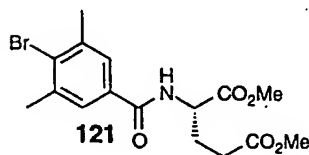
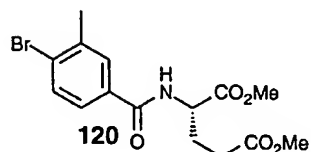
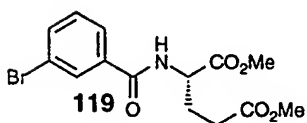
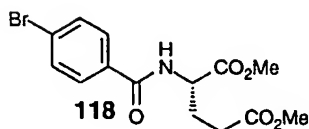




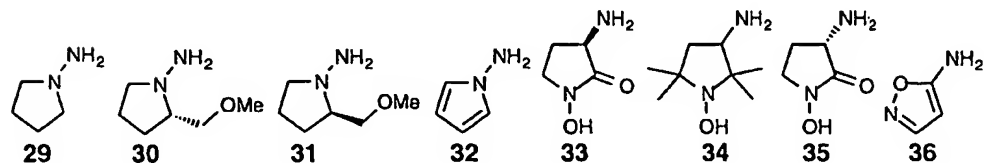
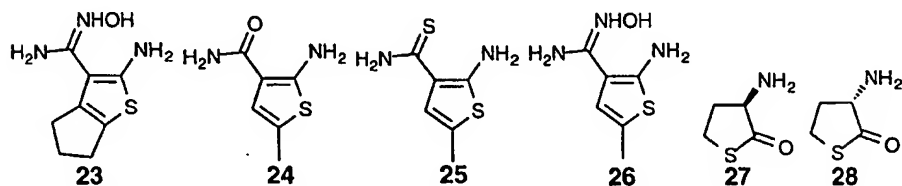
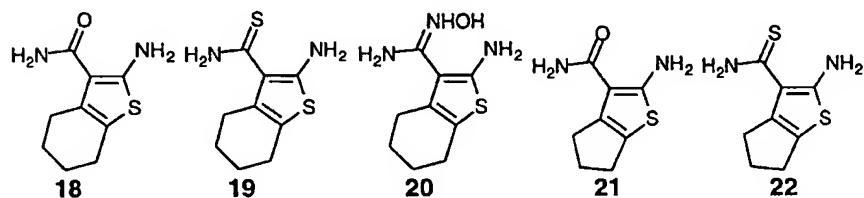
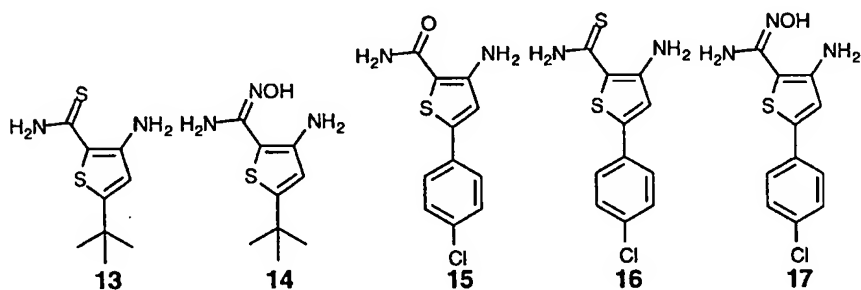
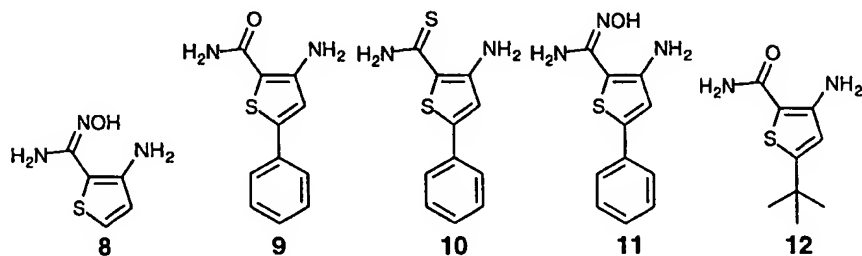
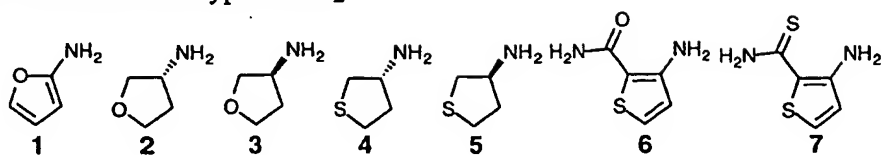
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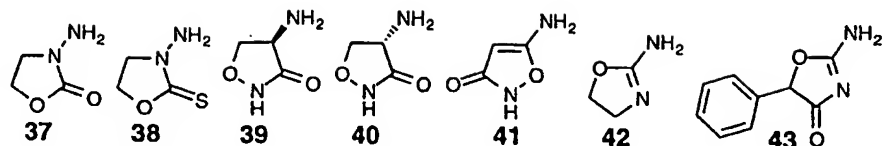


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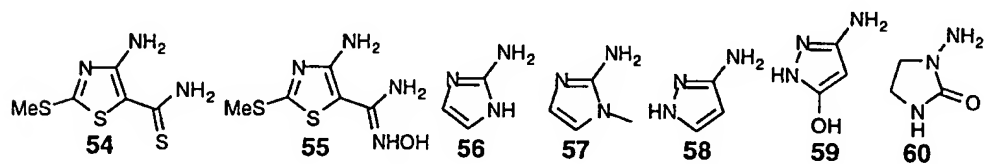
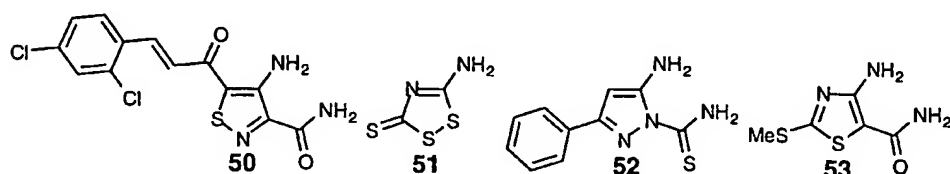
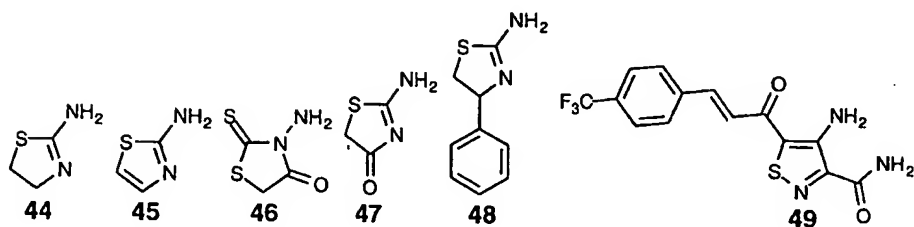


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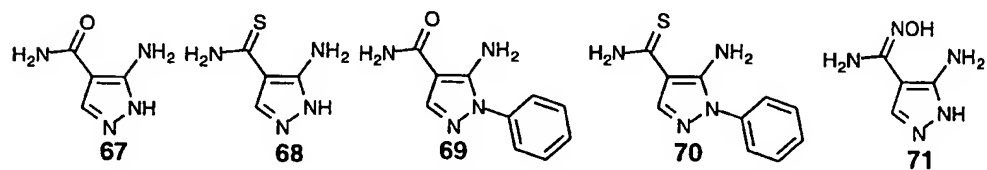
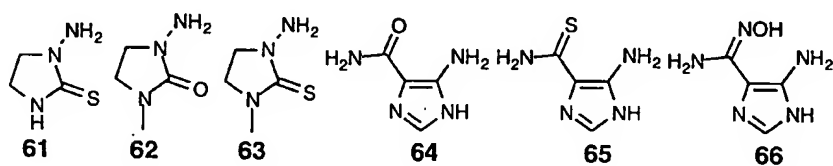
Table 12. Amines of the type A-NH₂



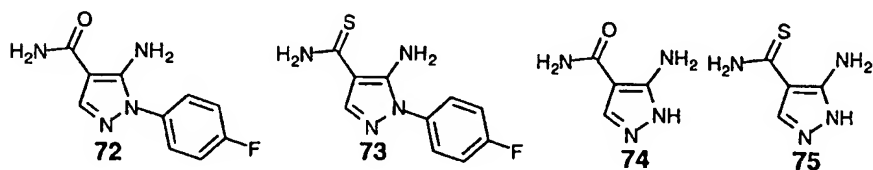
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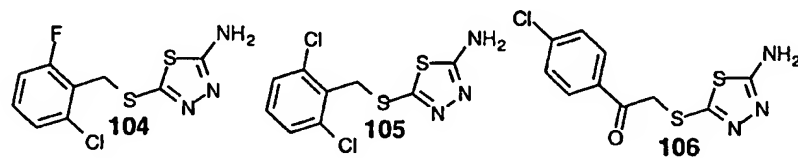
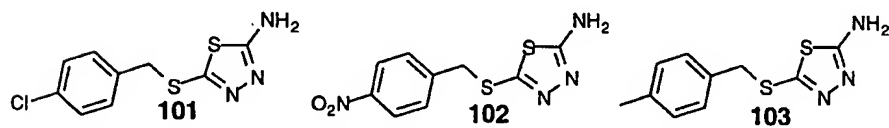
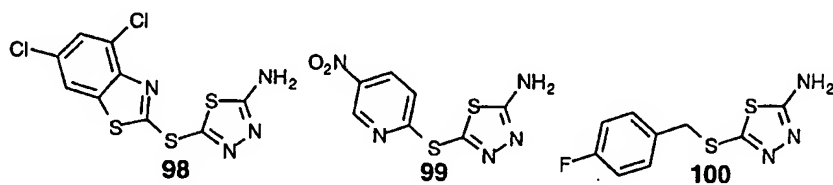
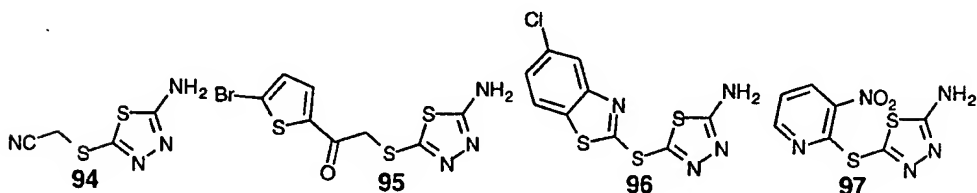
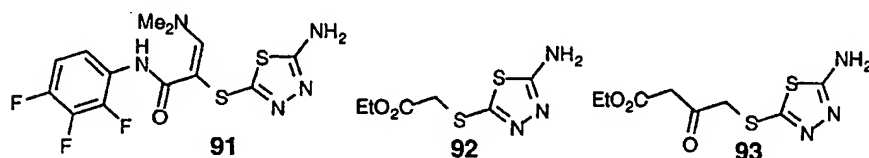
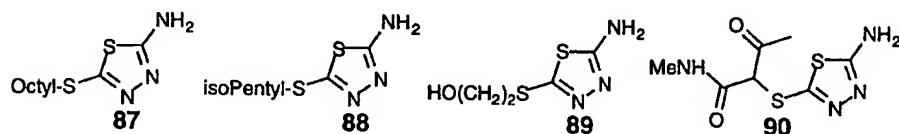
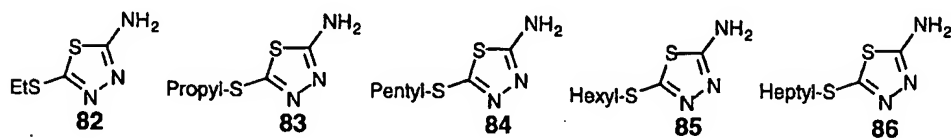
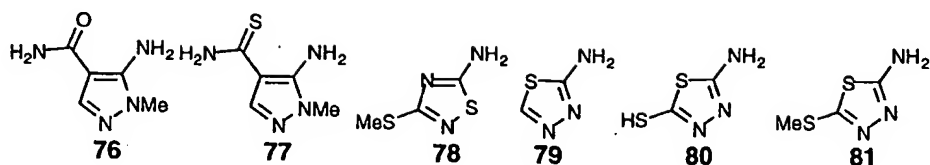


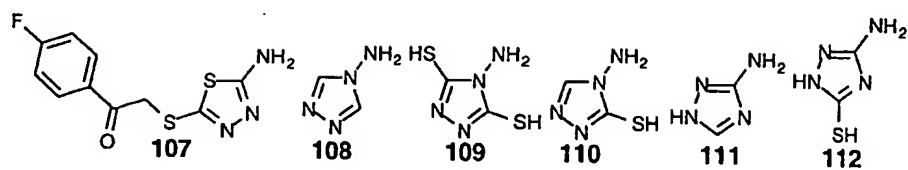
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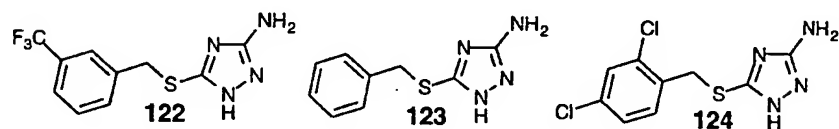
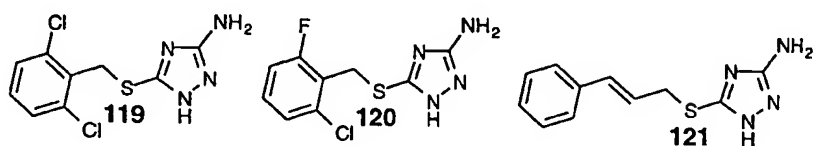
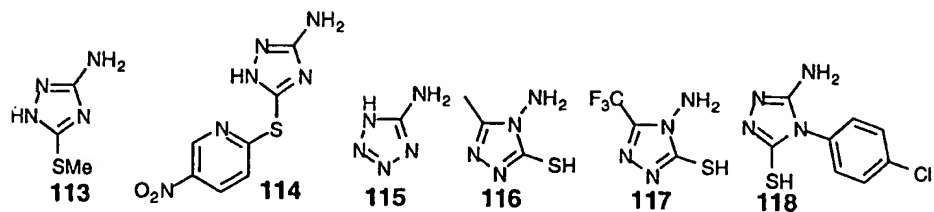
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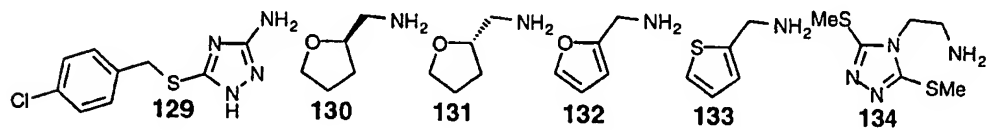
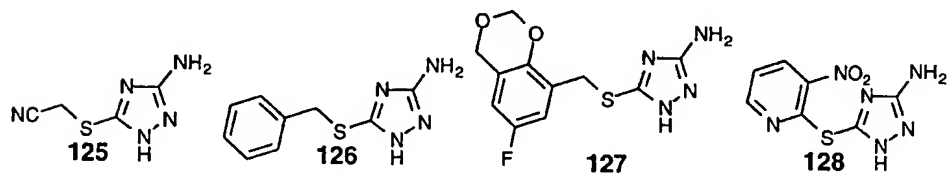




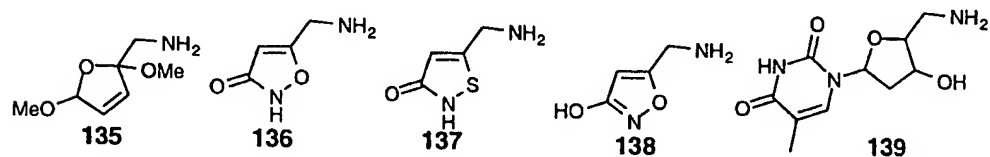
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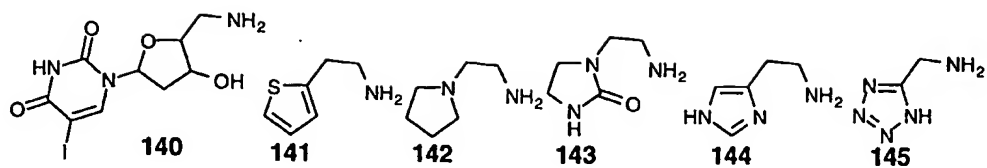


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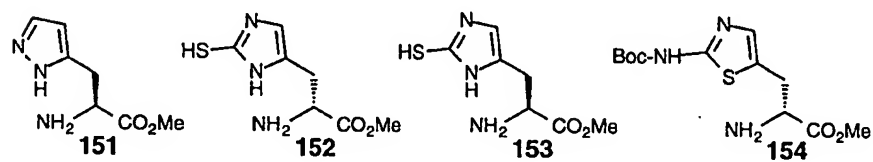
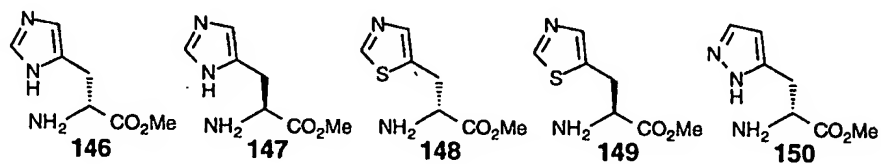


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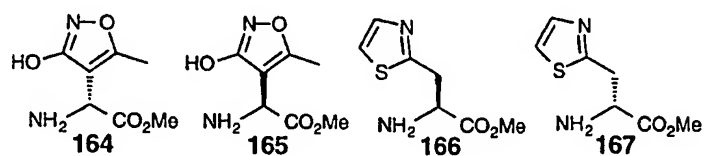
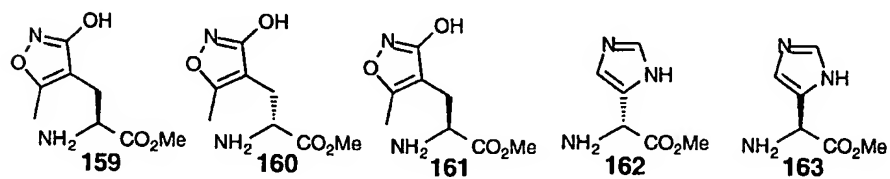
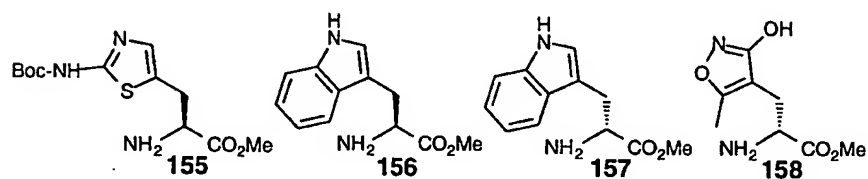




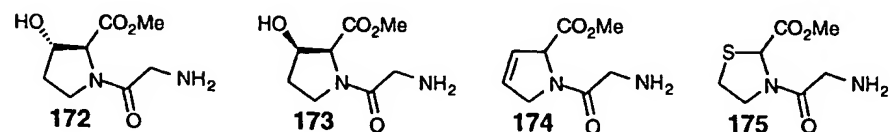
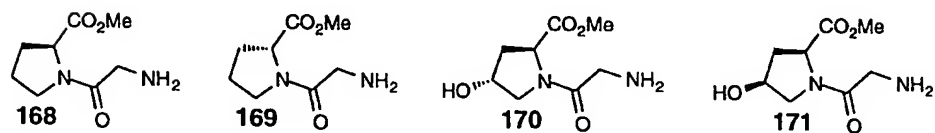
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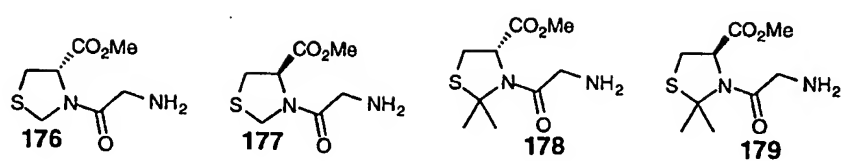


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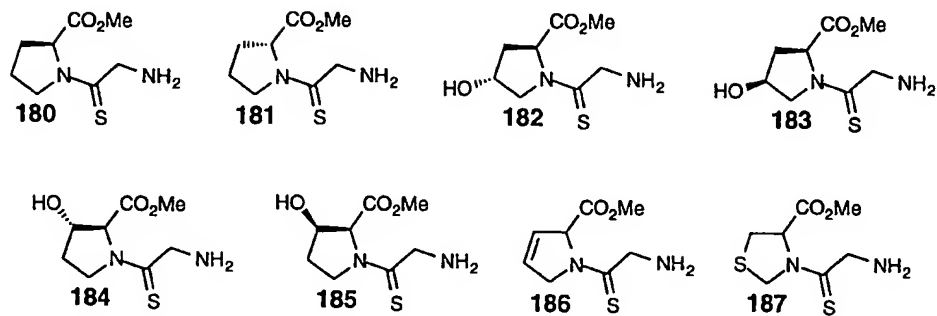


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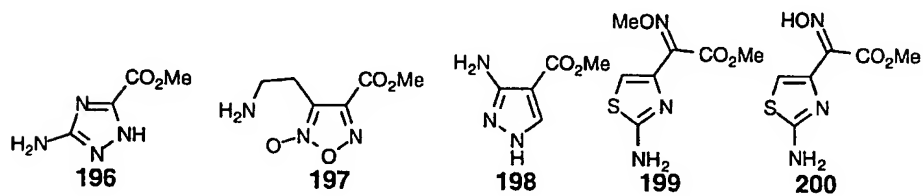
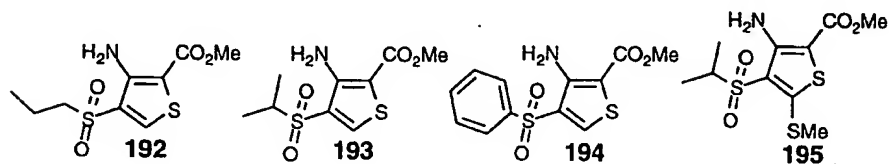
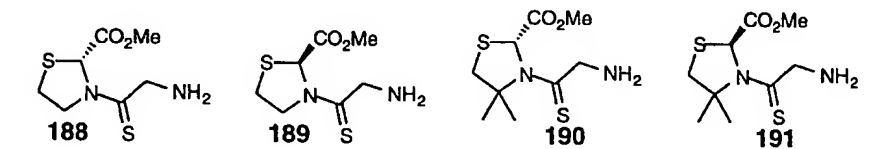




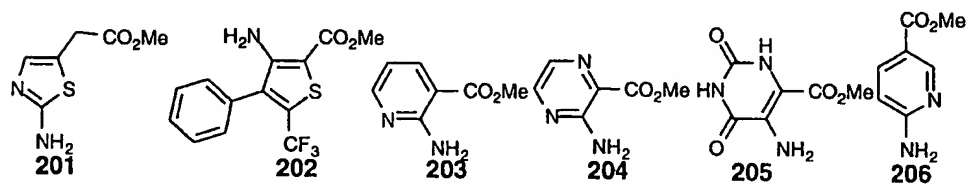
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2690



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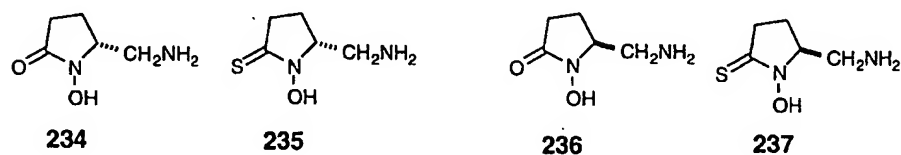
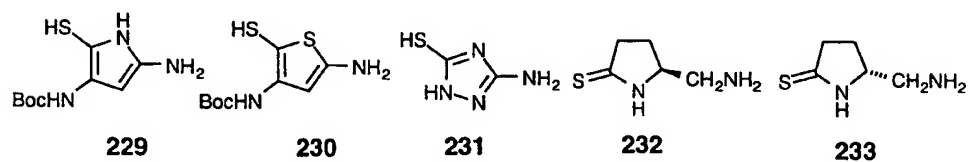
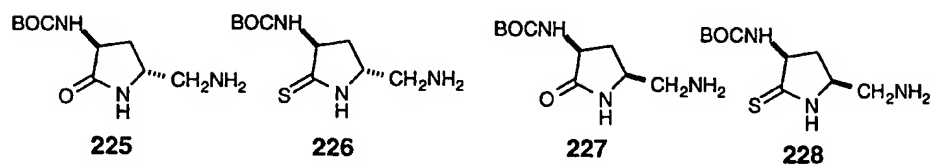
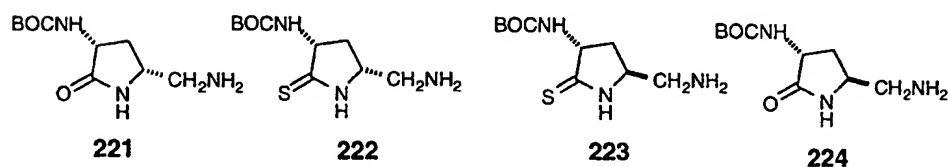
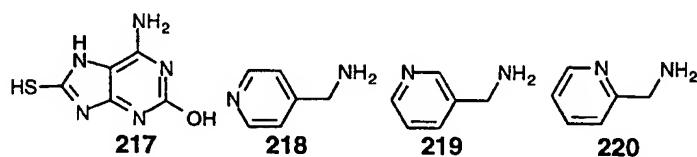
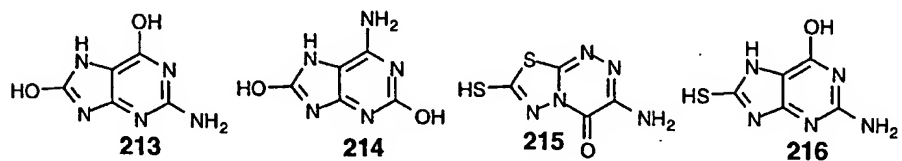
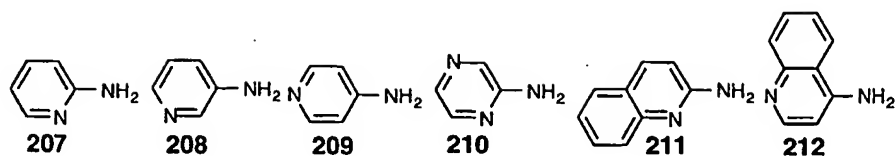
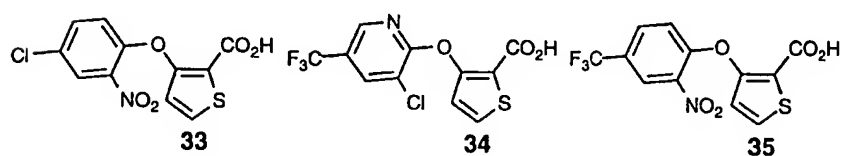
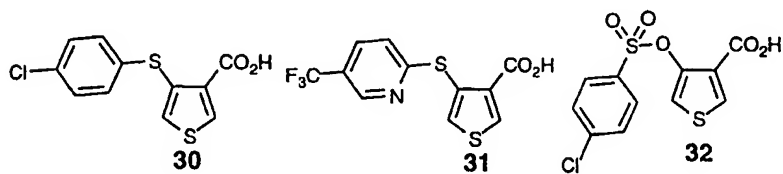
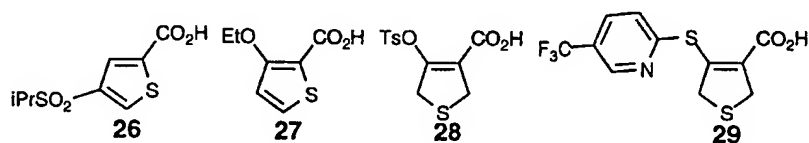
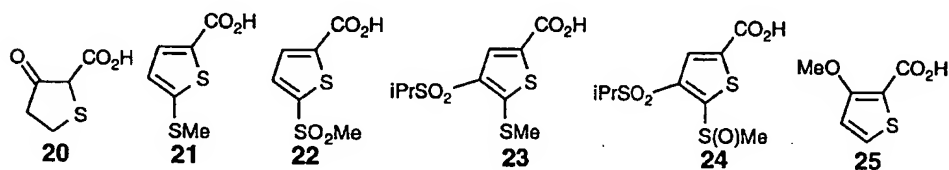
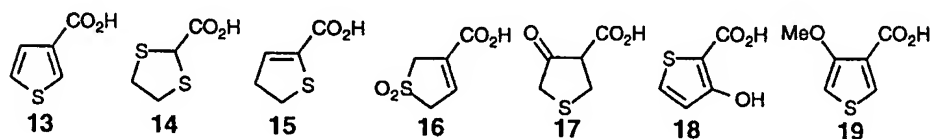
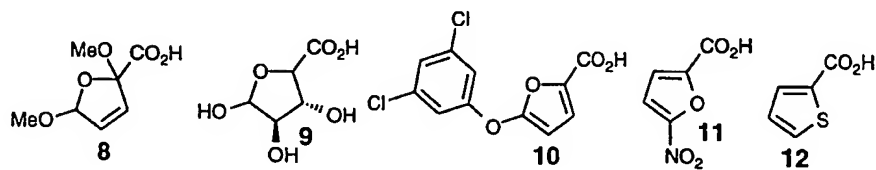
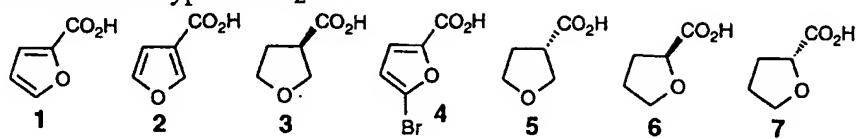
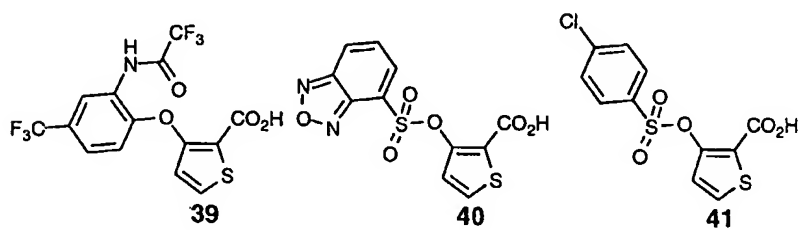
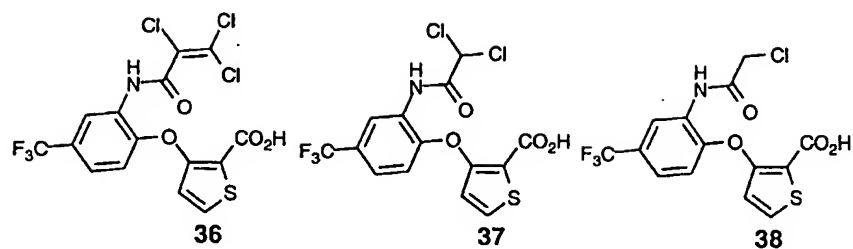
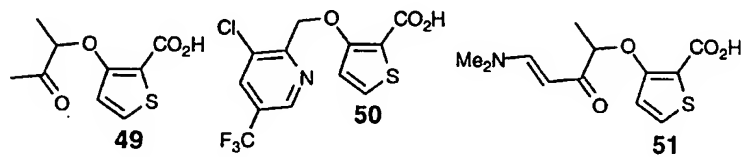
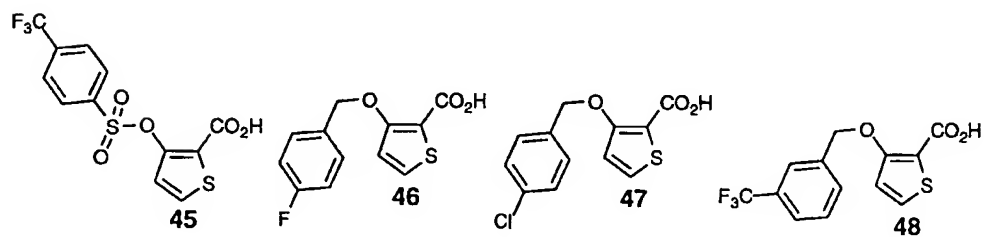
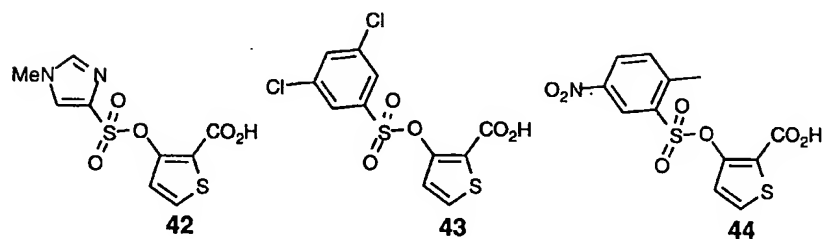


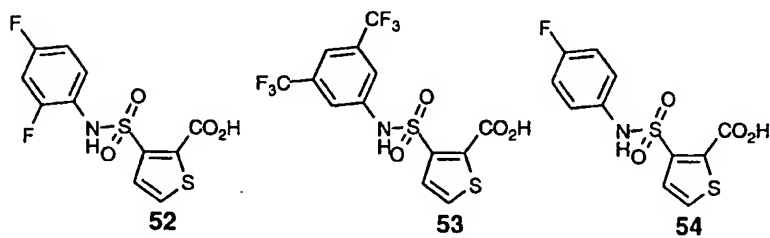
Table 13. Acids of the type A-CO₂H

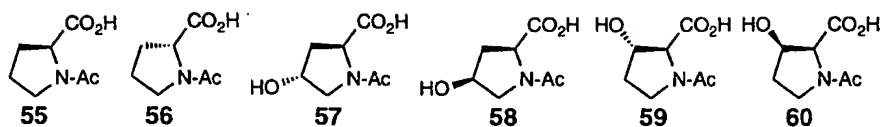


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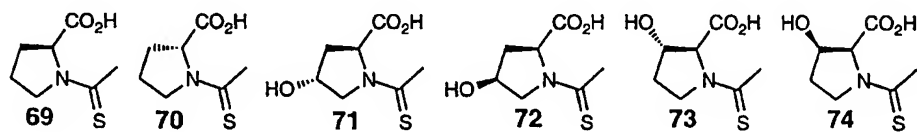
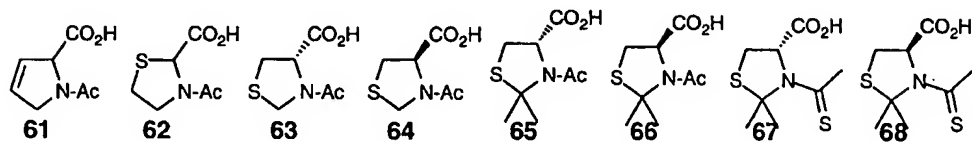


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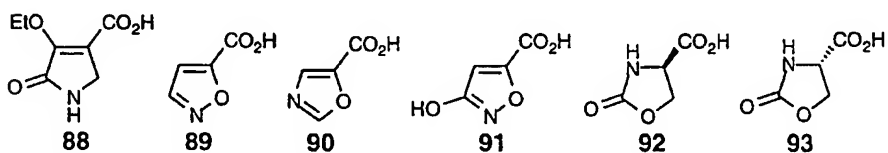
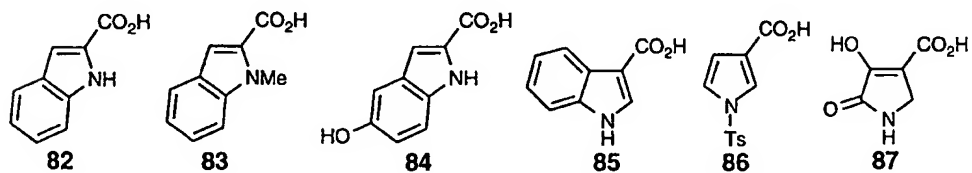
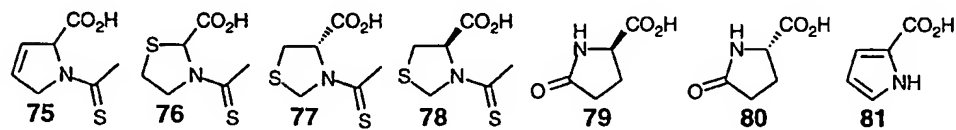




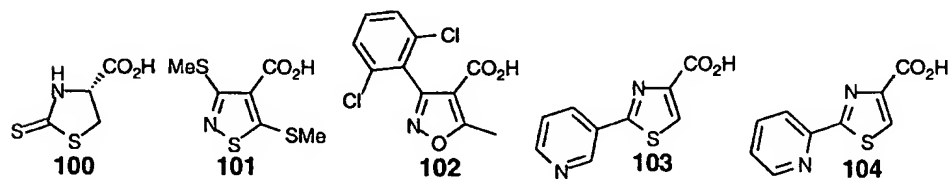
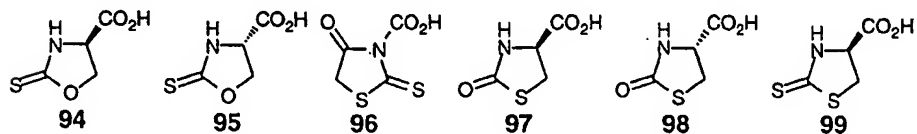
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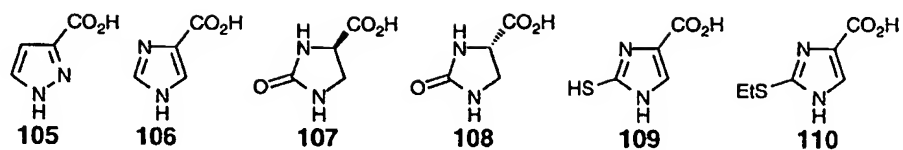
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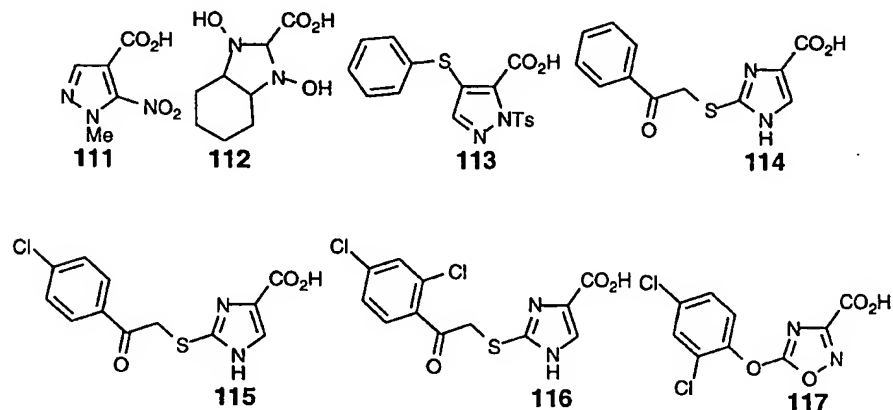
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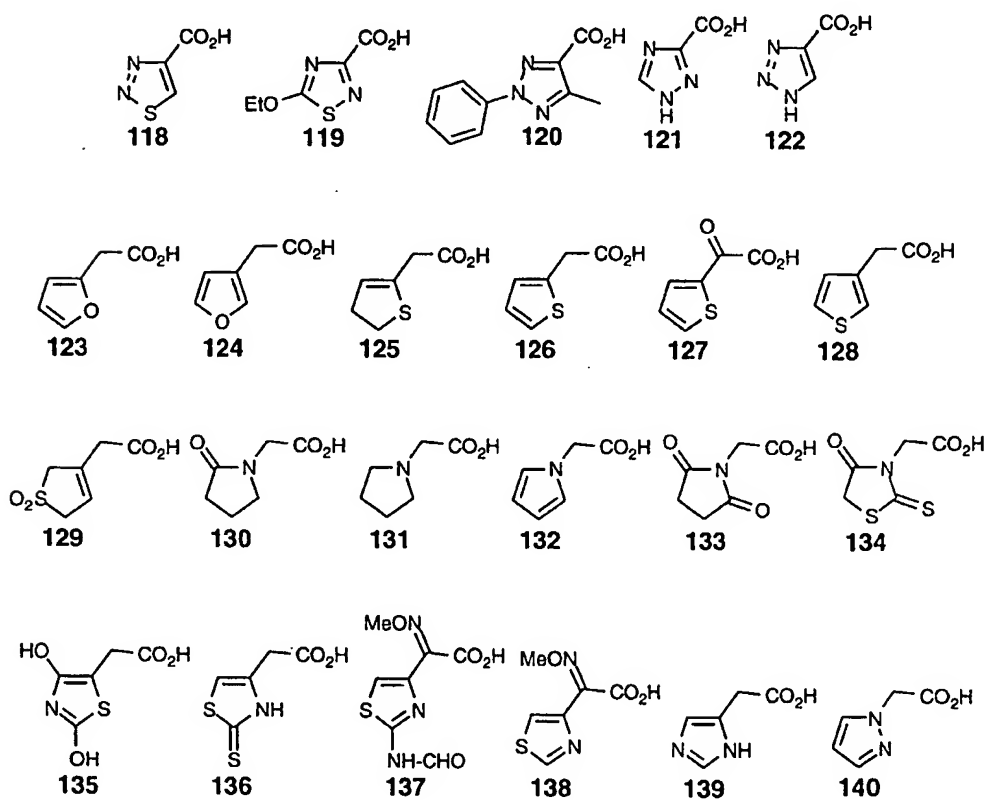
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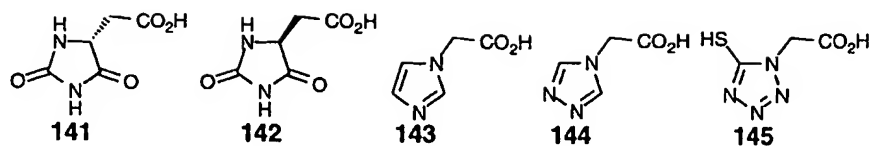


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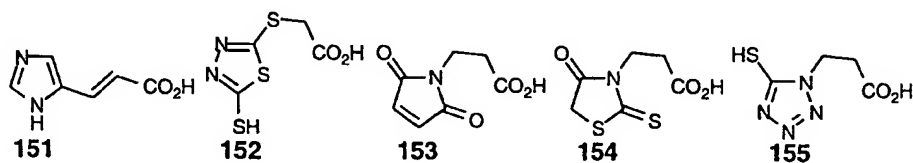
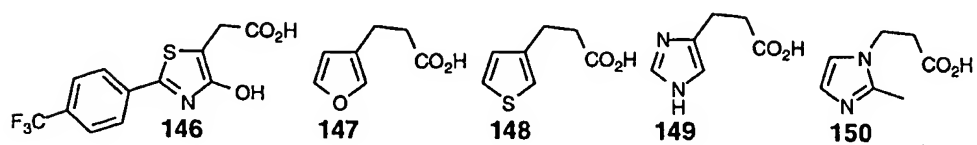


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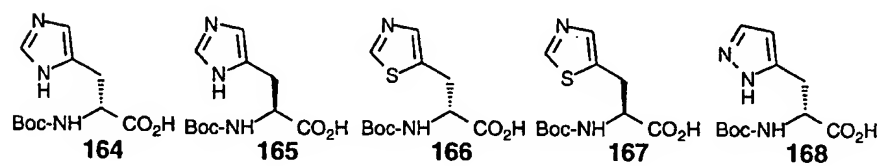
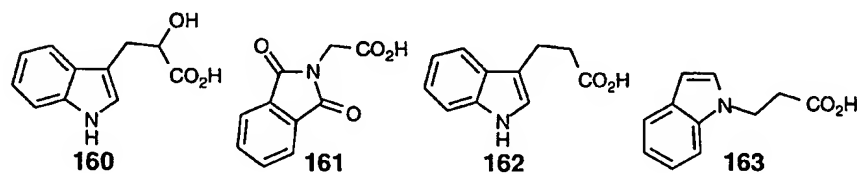
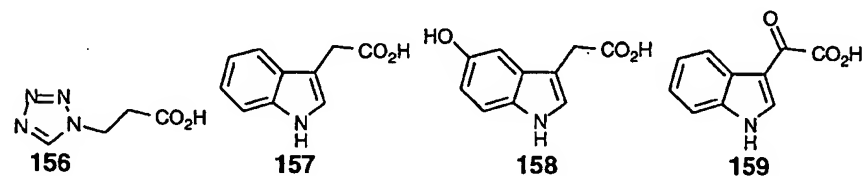




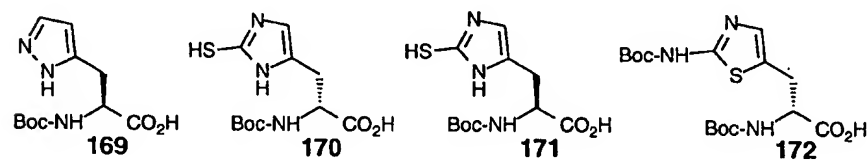
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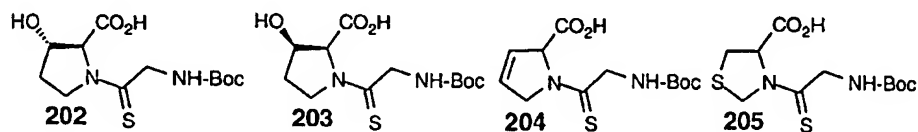
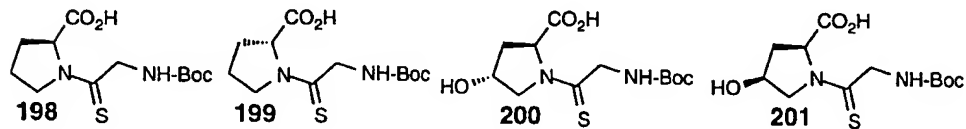
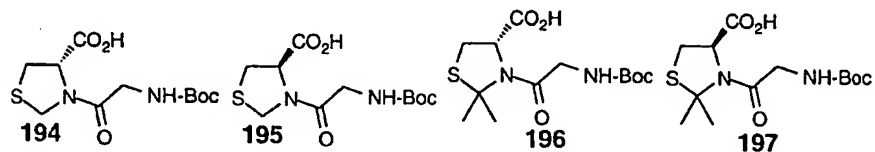
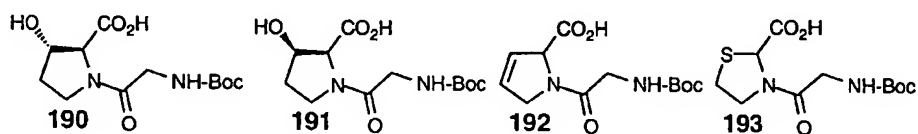
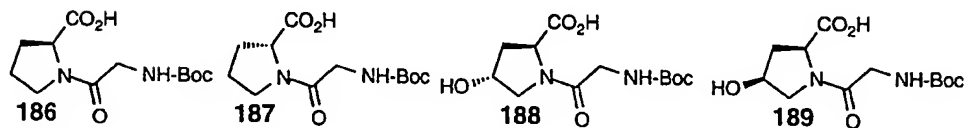
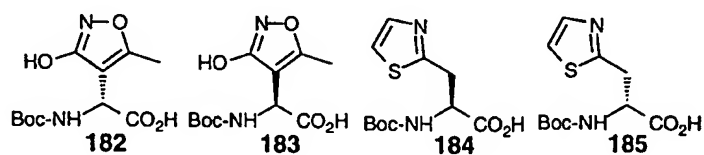
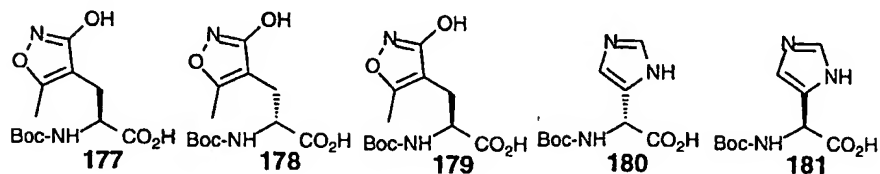
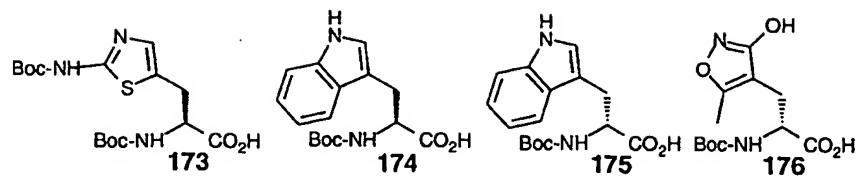


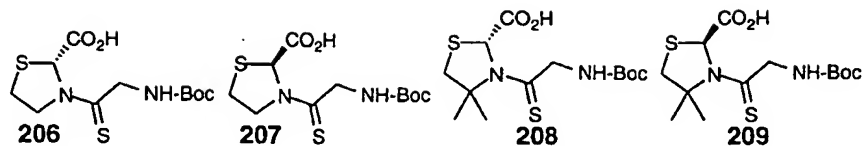
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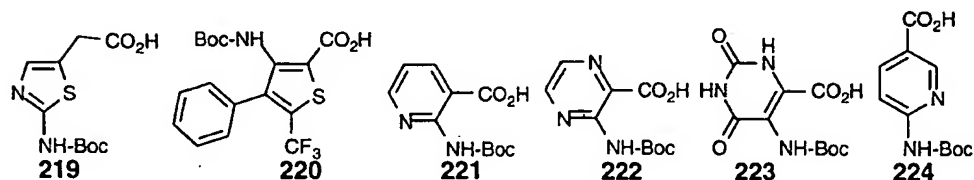
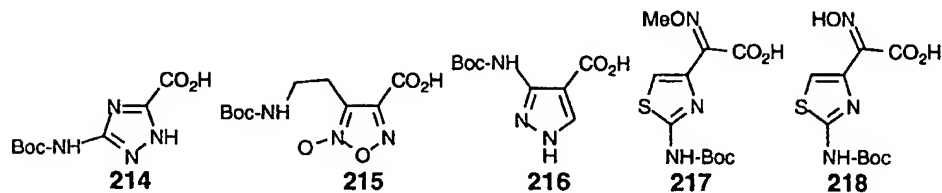
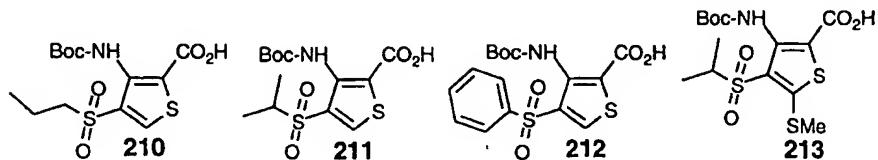
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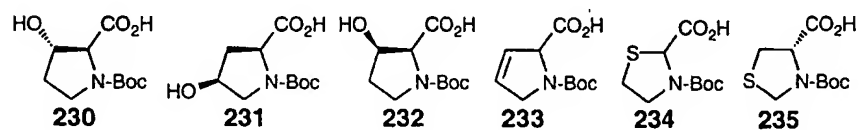
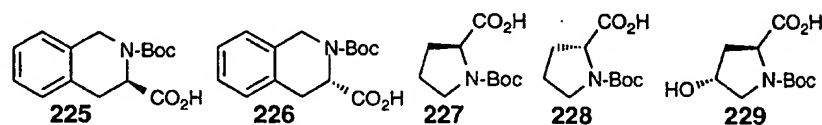




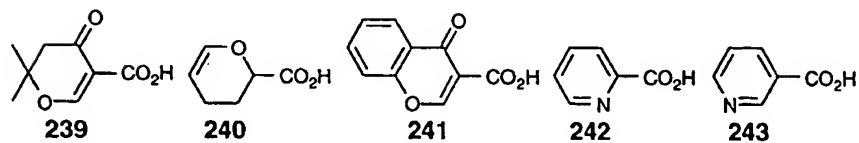
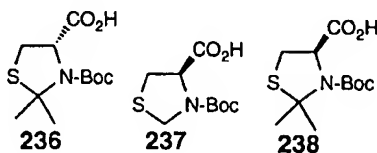
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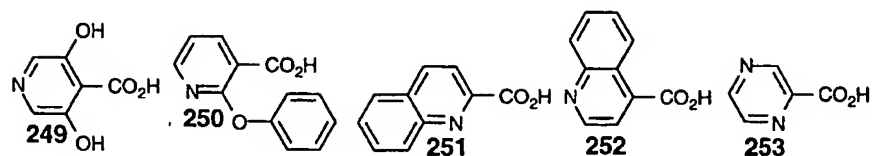
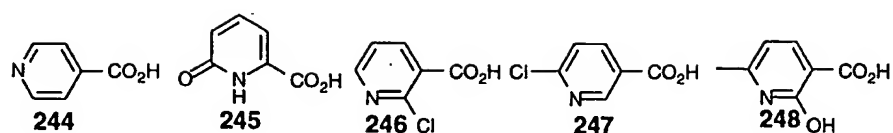
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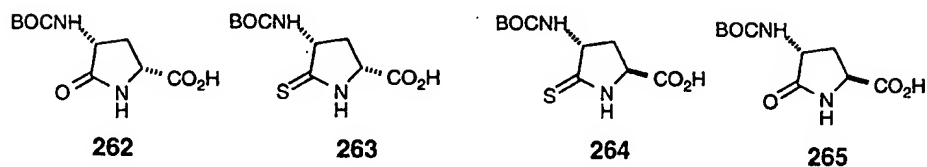
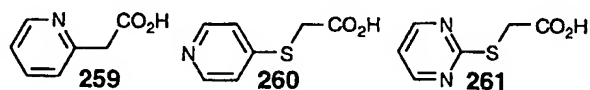
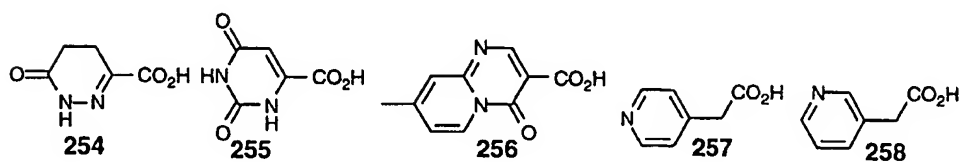
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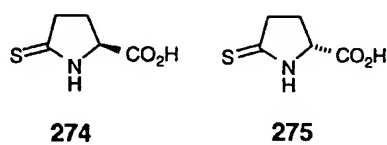
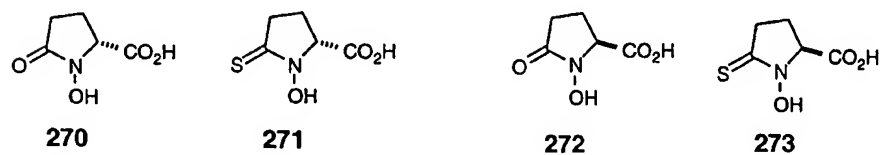
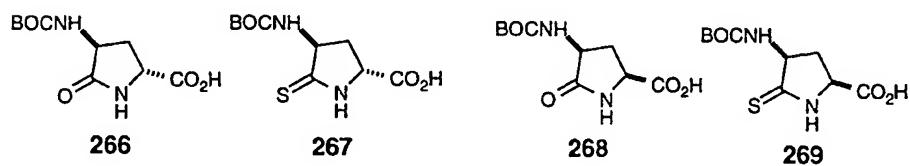
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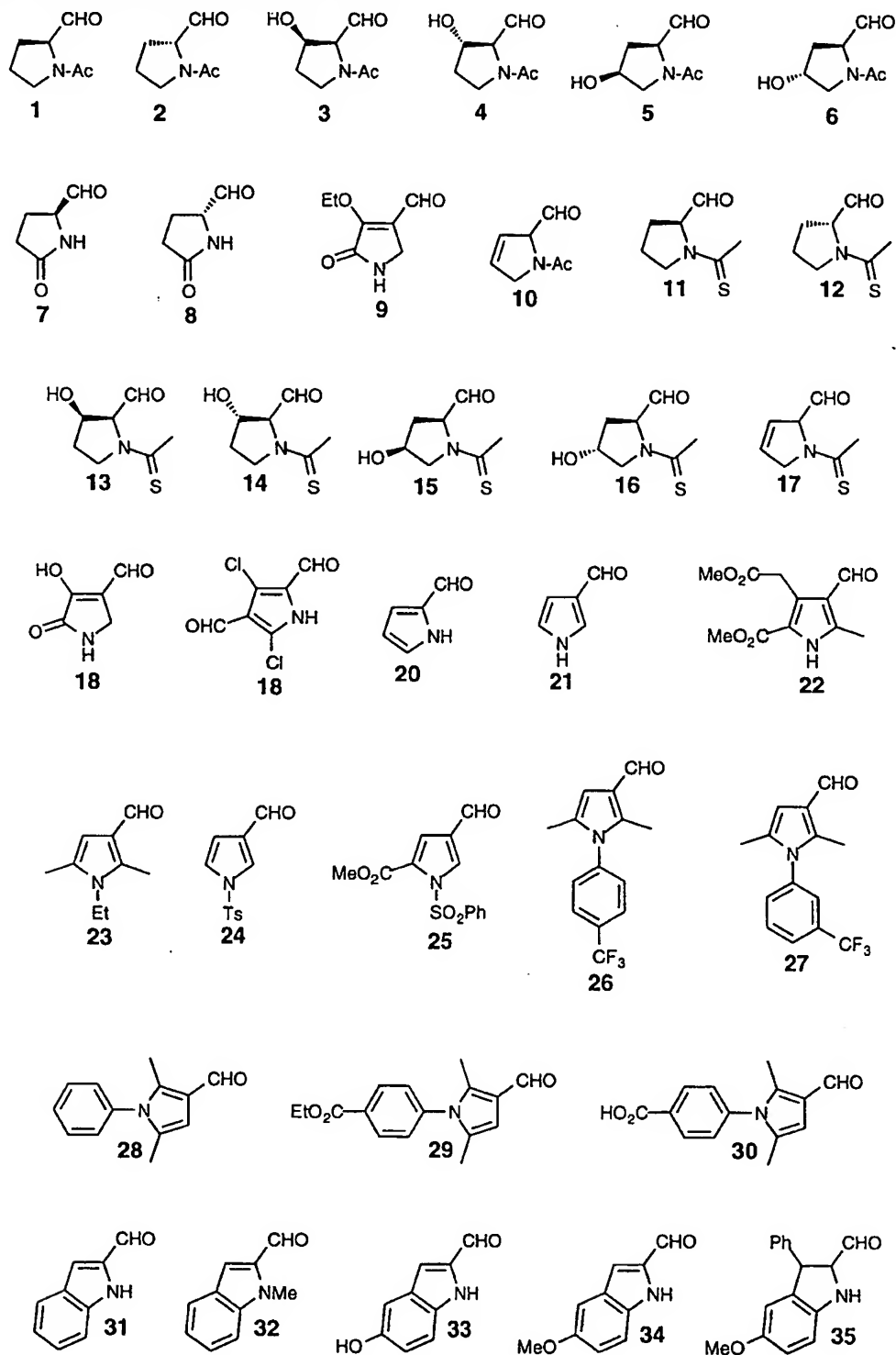


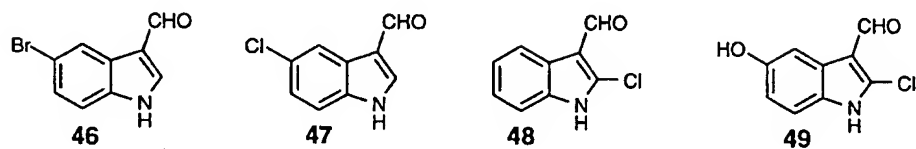
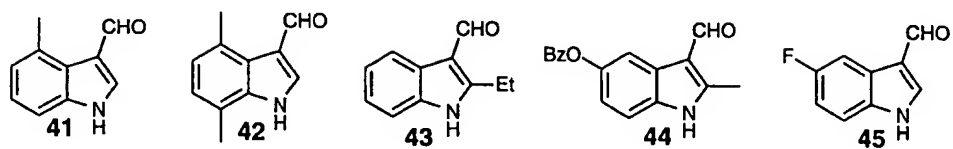
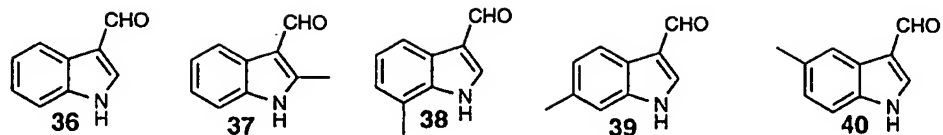
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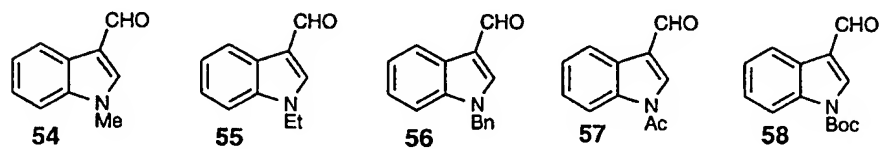
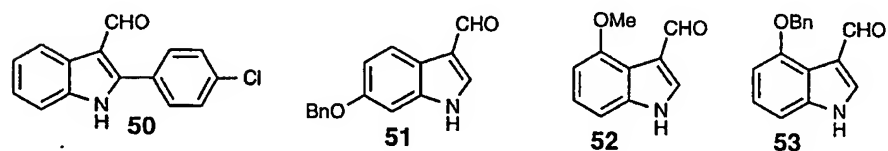
2830

Table 14. Aldehydes of the type A-CHO

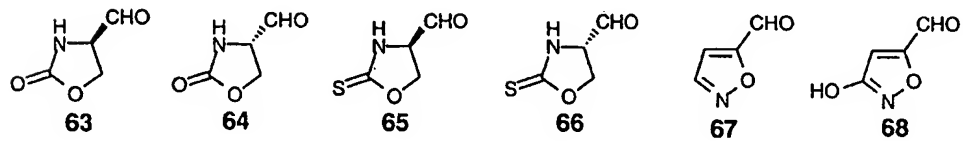
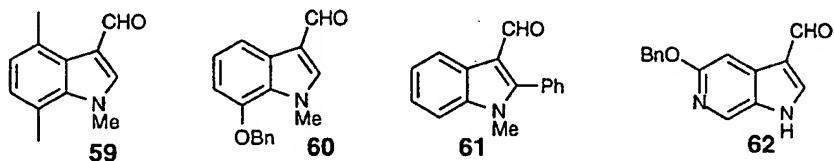


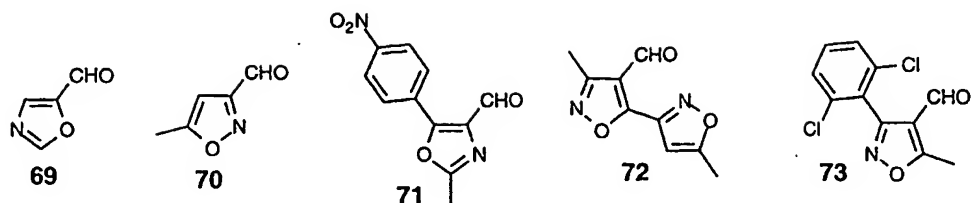


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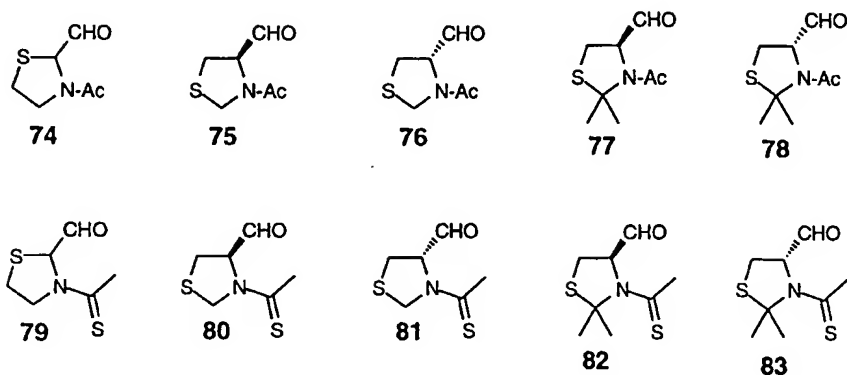


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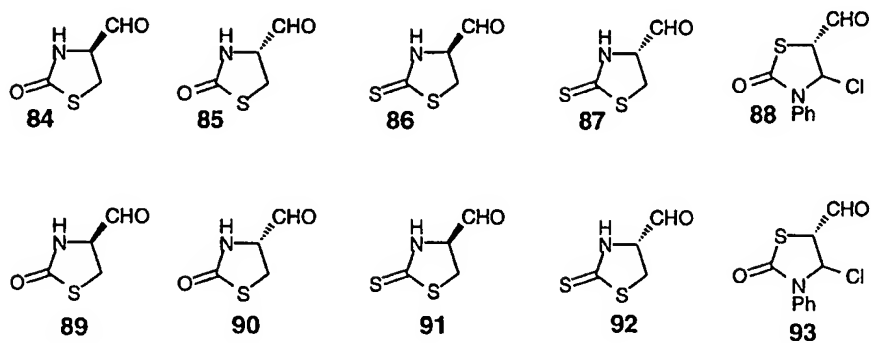




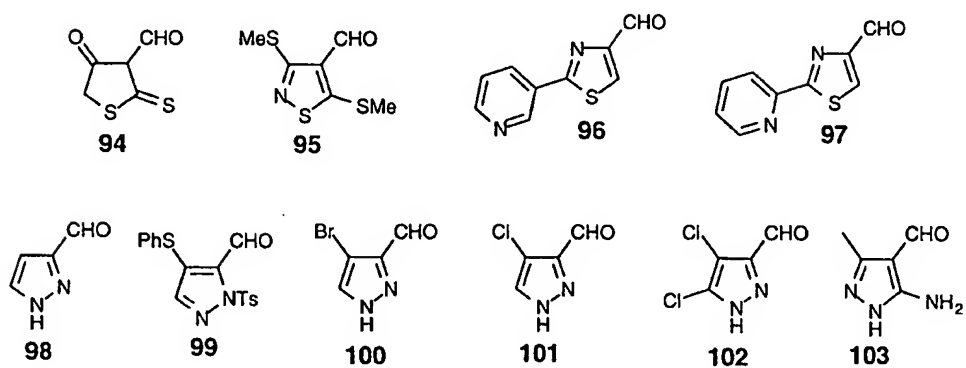
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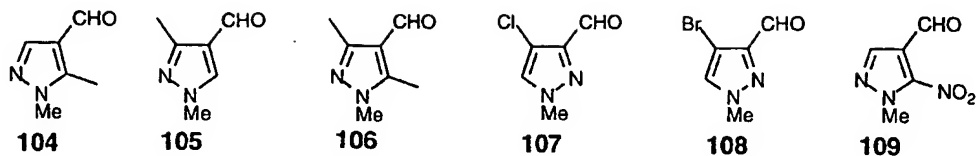


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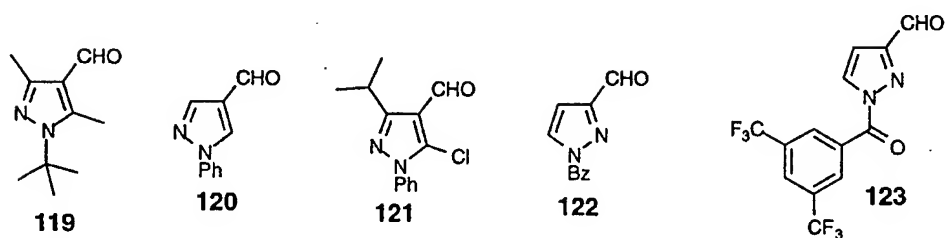
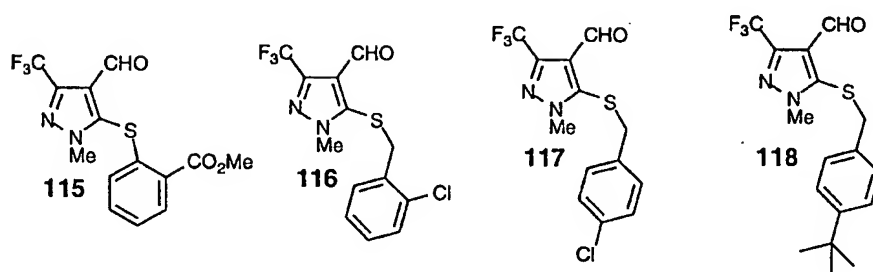
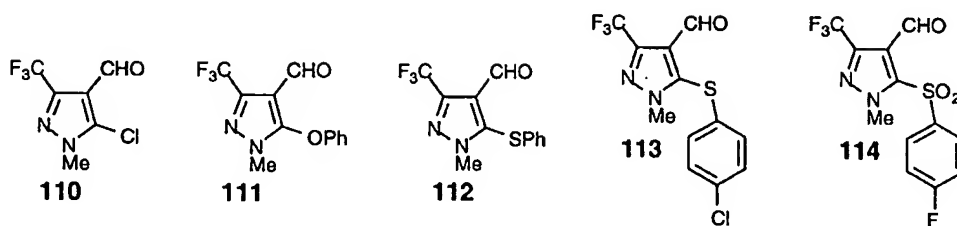


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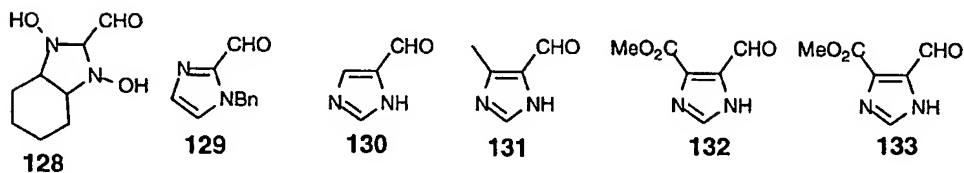
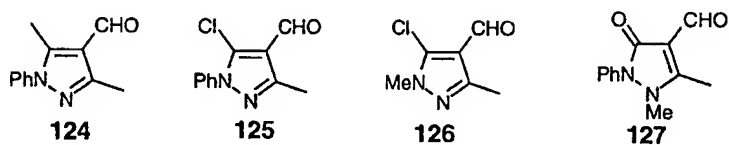




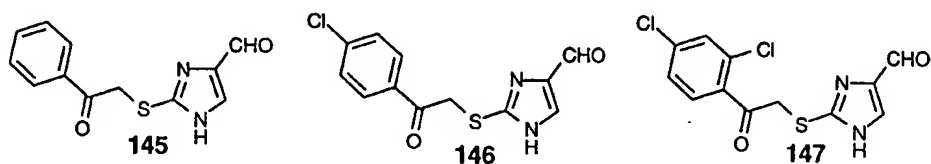
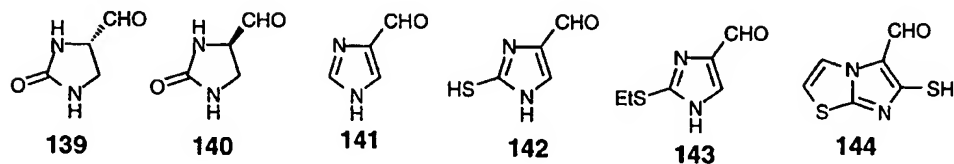
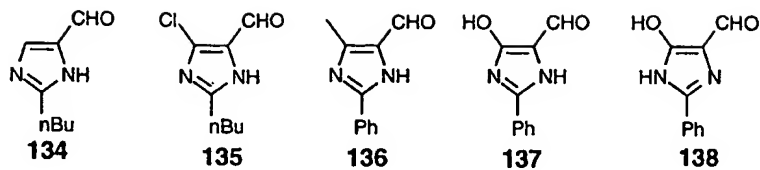
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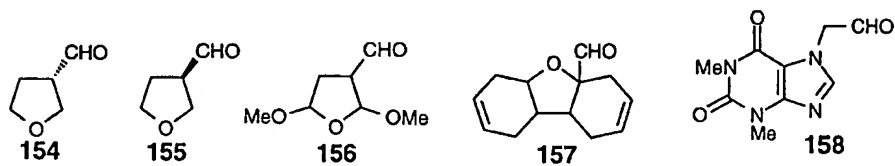
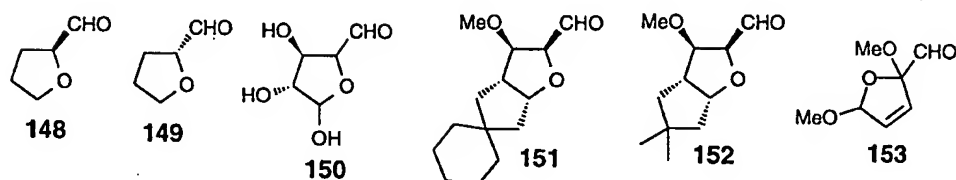
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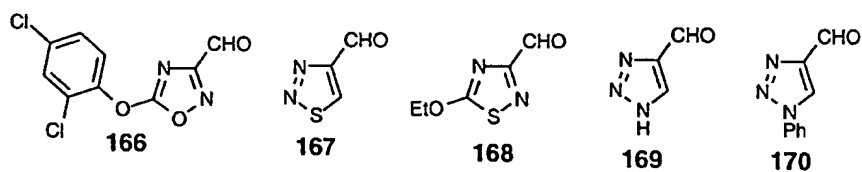
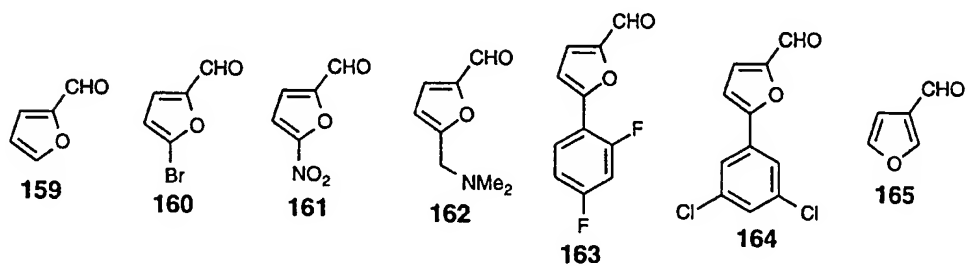
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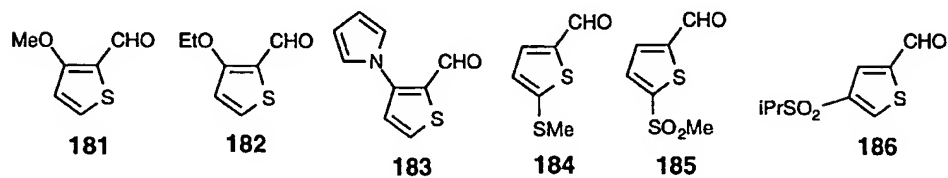
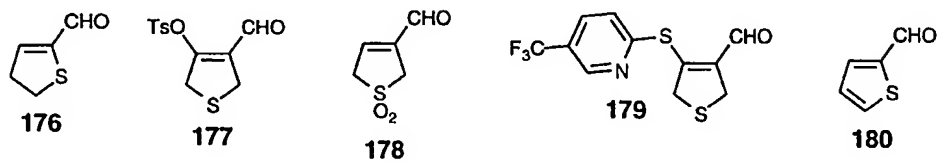
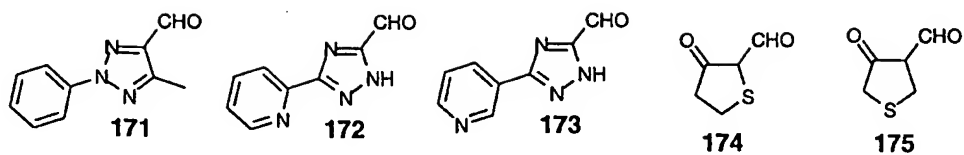
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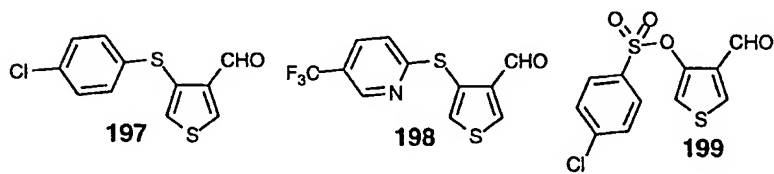
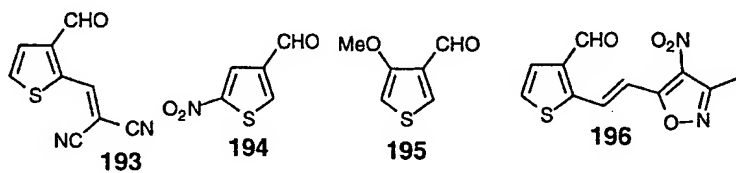
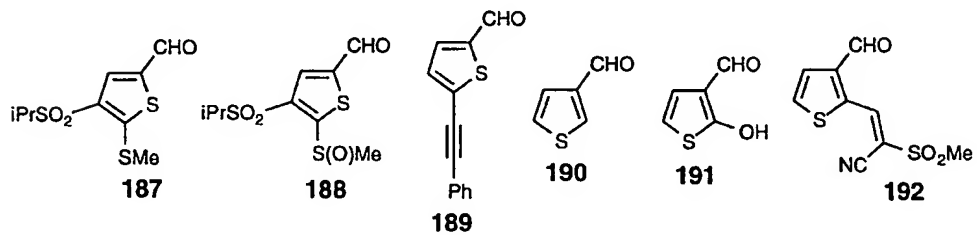
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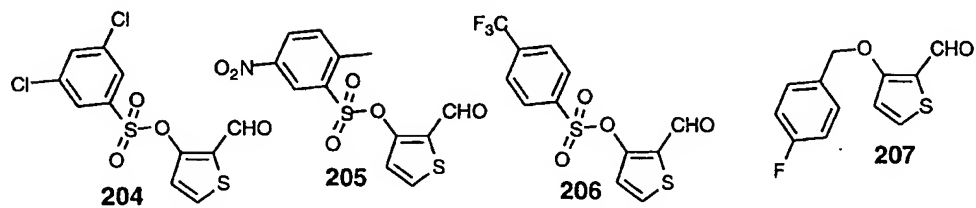
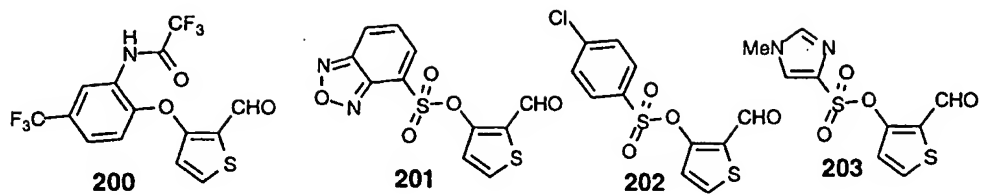
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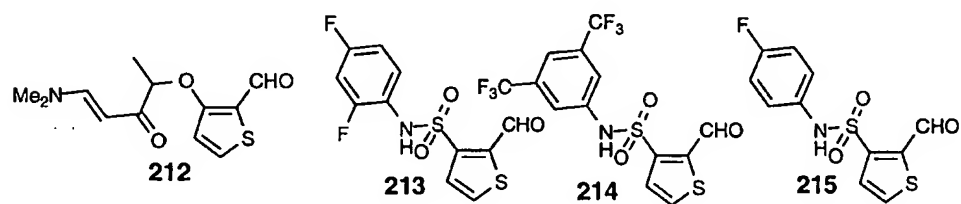
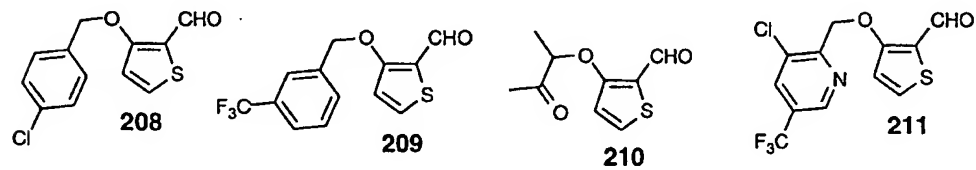
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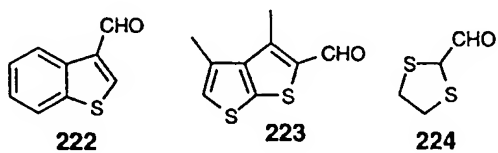
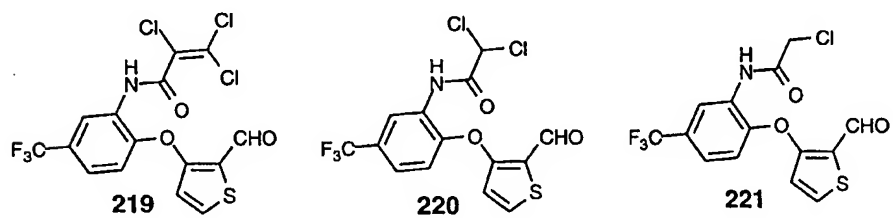
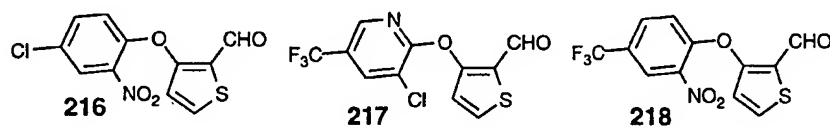
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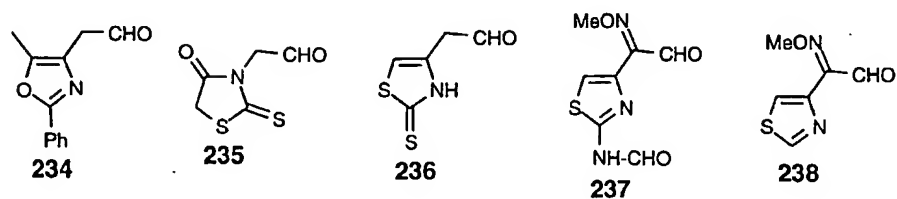
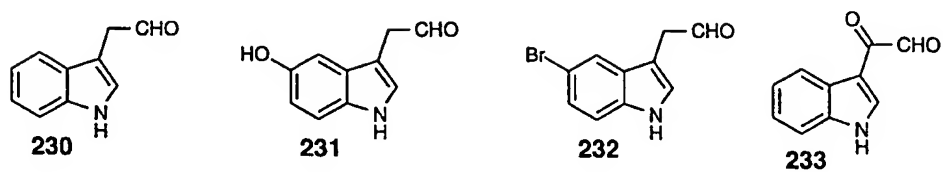
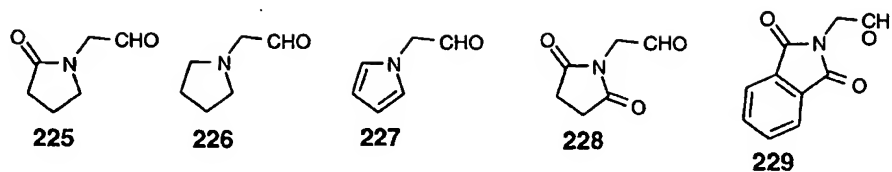
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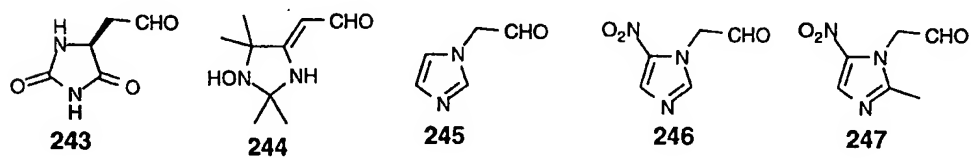
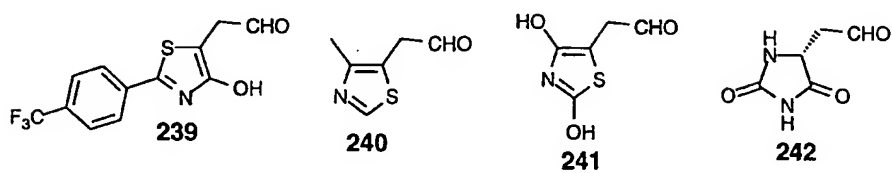
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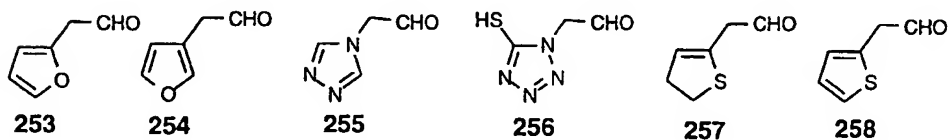
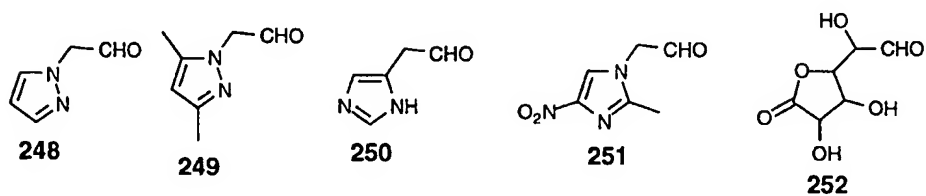
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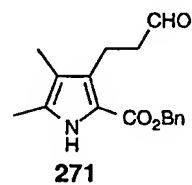
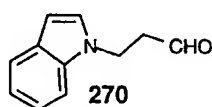
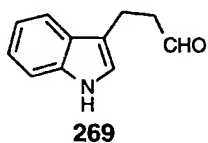
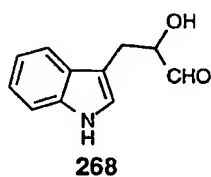
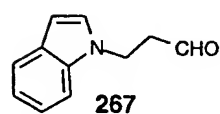
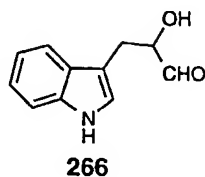
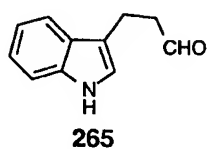
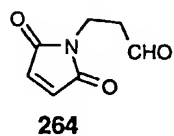
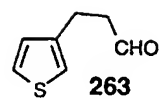
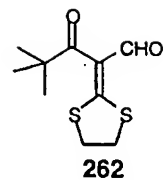
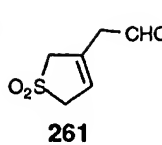
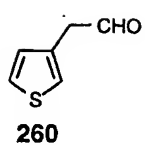
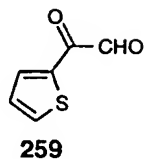
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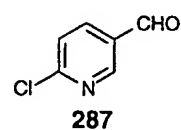
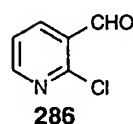
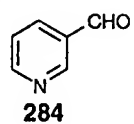
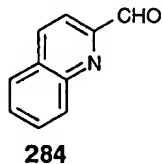
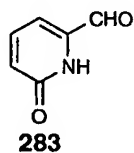
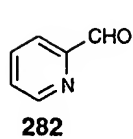
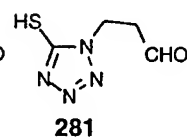
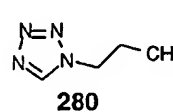
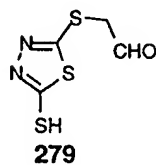
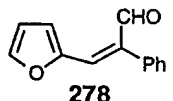
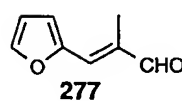
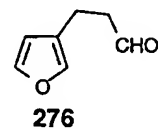
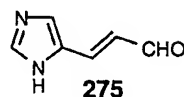
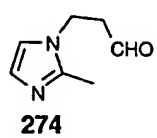
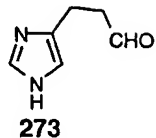
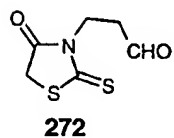
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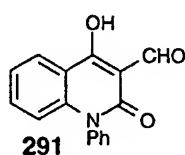
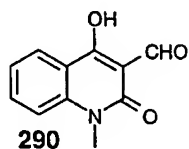
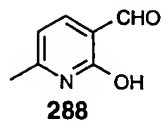
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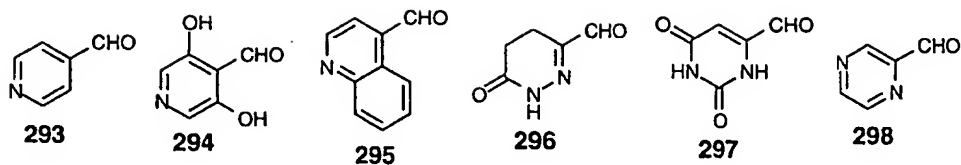


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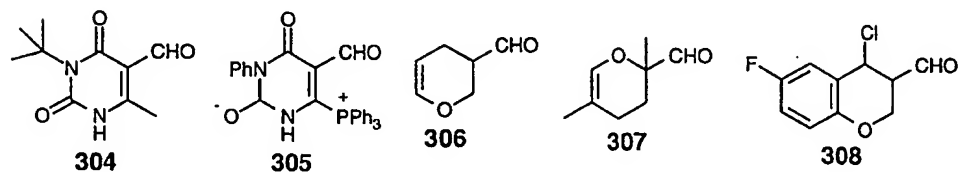
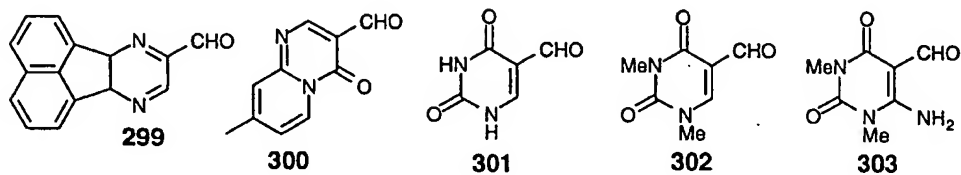


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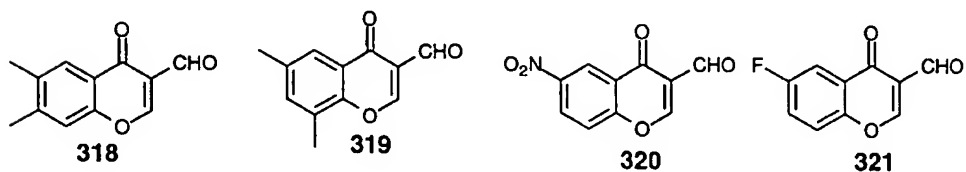
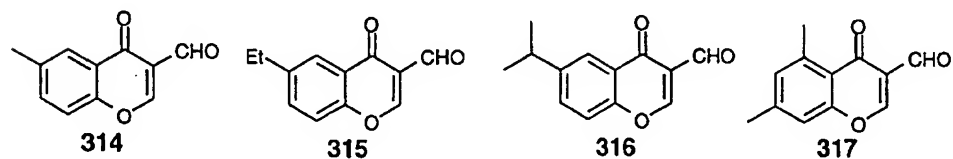
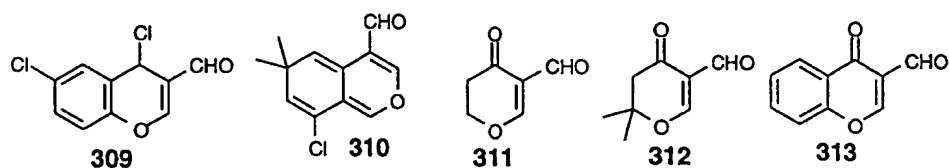




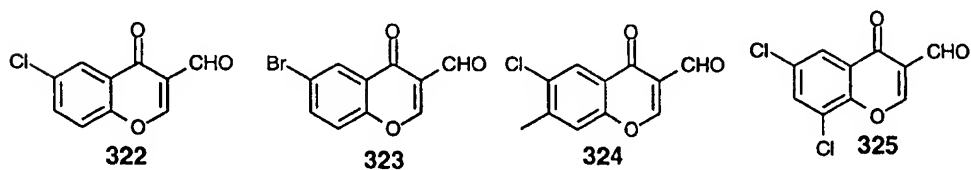
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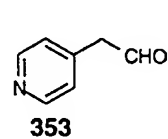
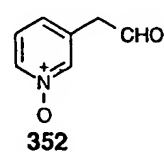
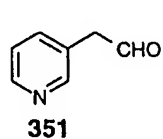
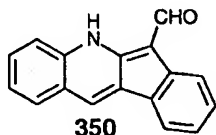
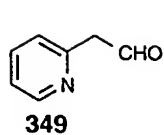
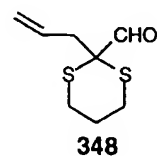
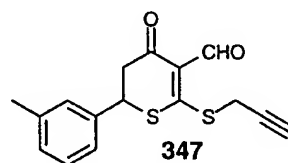
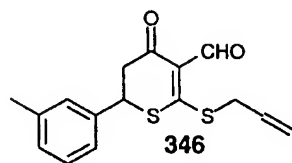
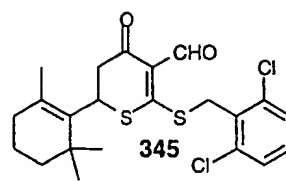
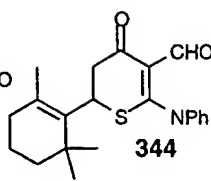
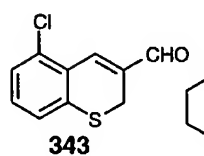
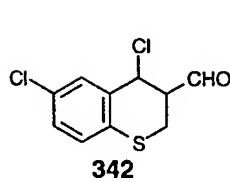
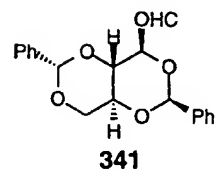
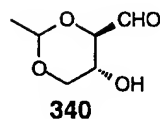
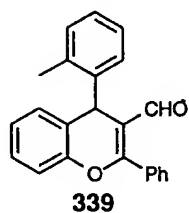
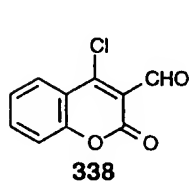
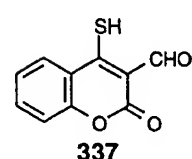
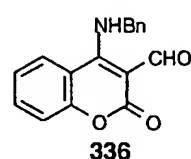
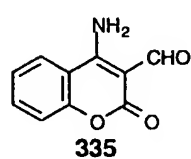
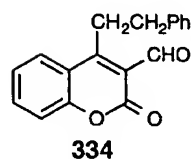
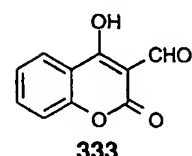
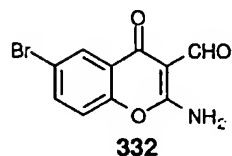
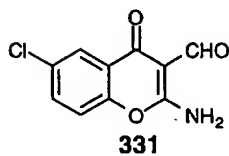
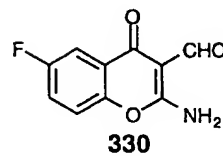
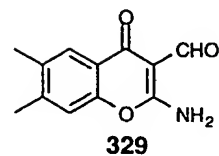
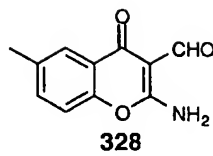
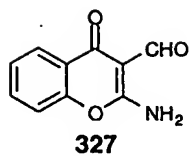
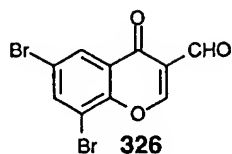


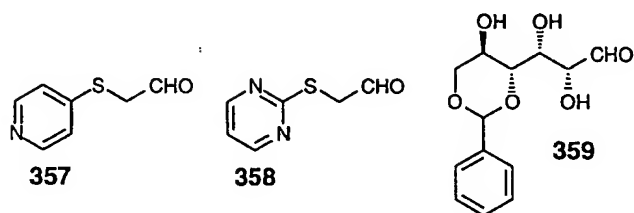
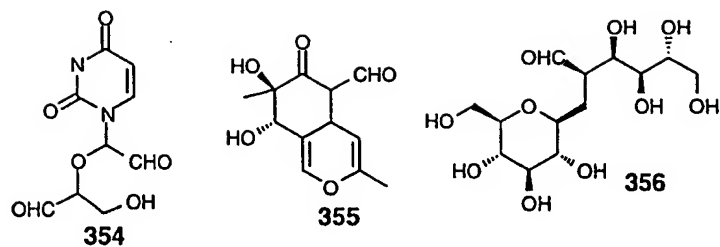
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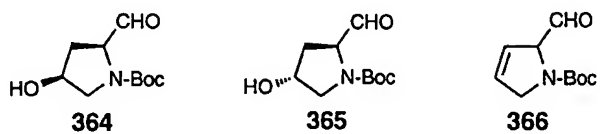
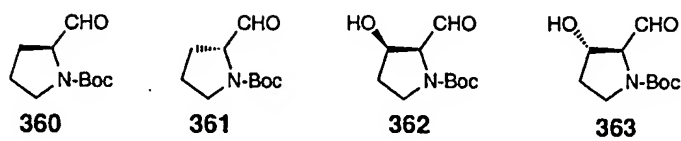
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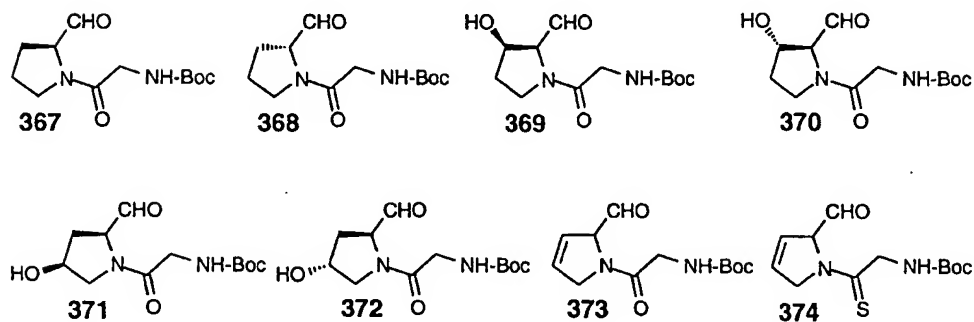




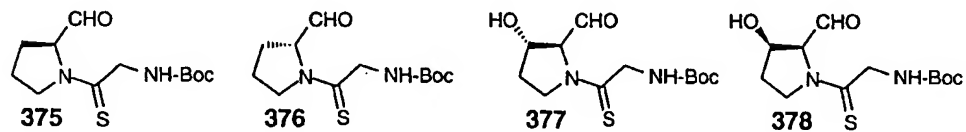
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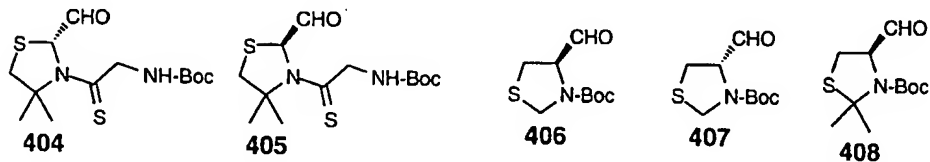
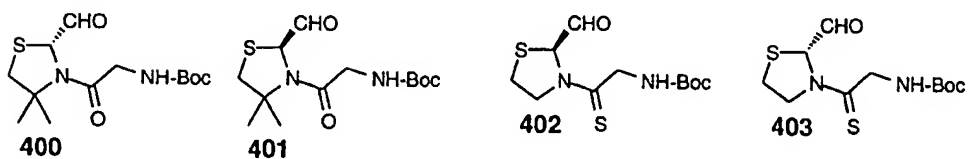
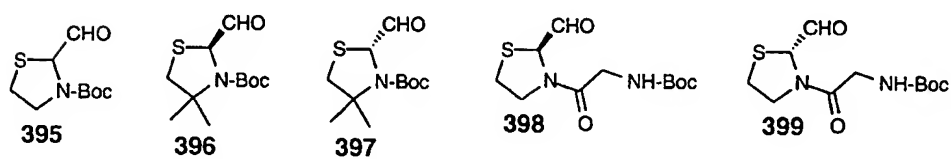
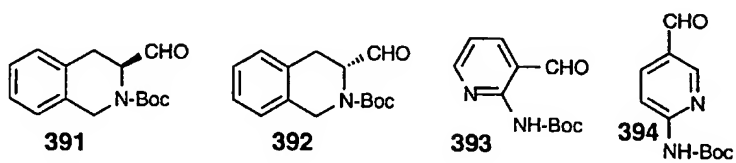
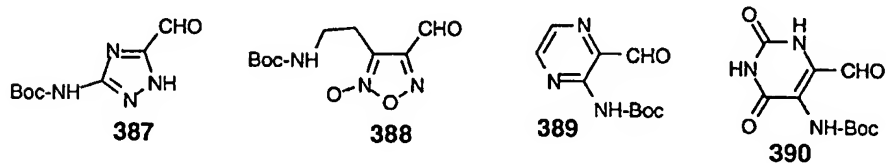
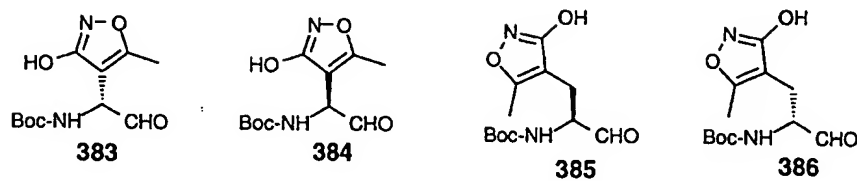
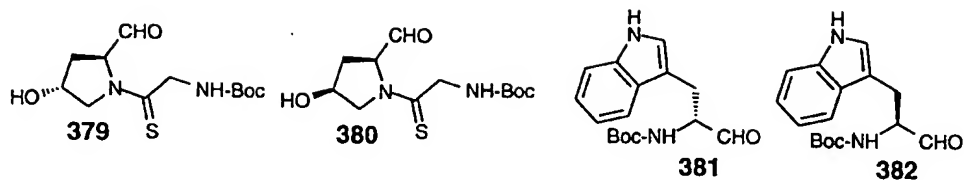


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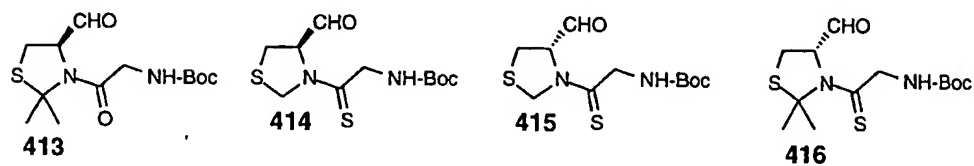
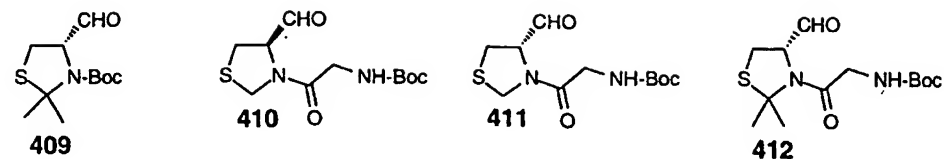


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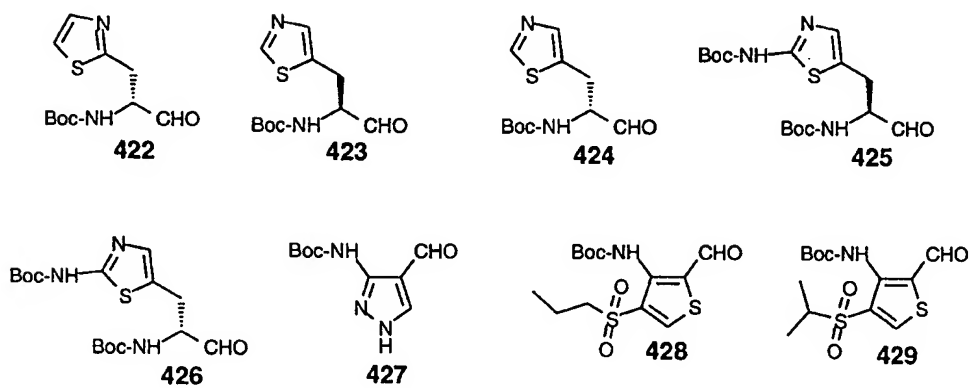
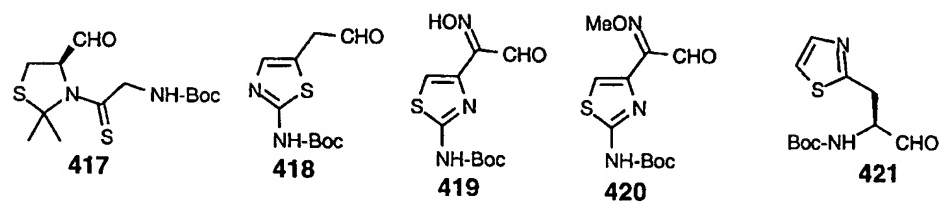




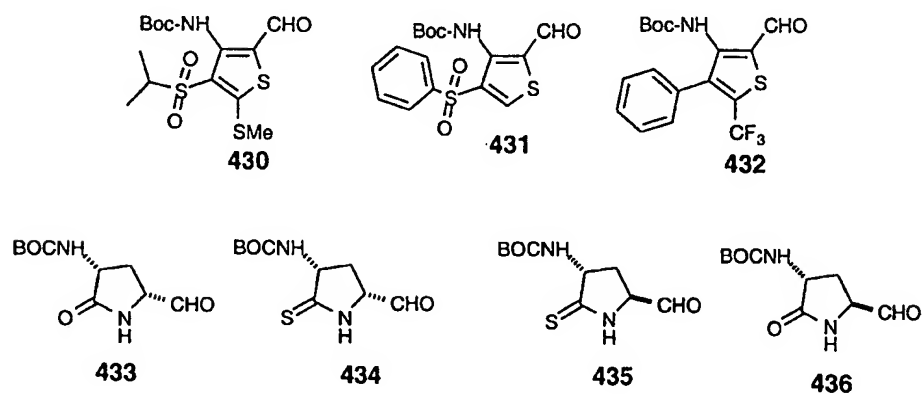
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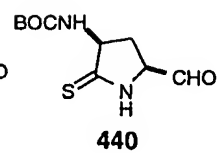
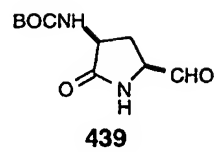
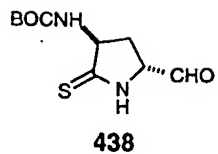
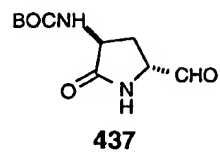


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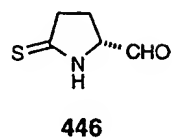
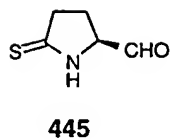
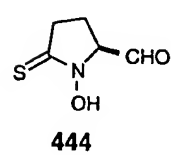
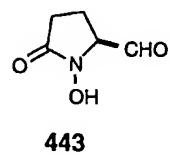
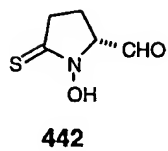
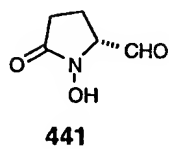
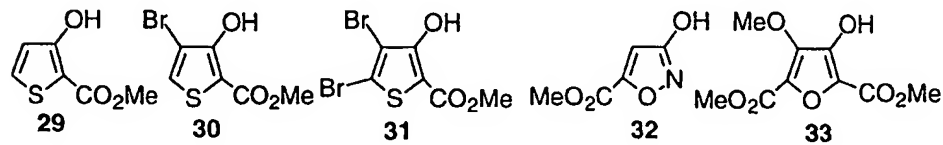
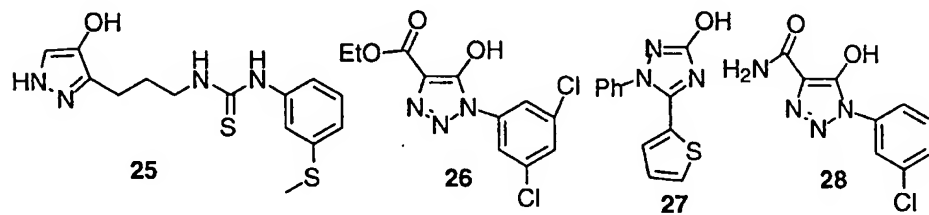
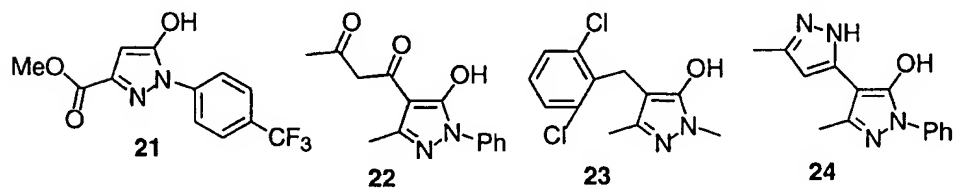
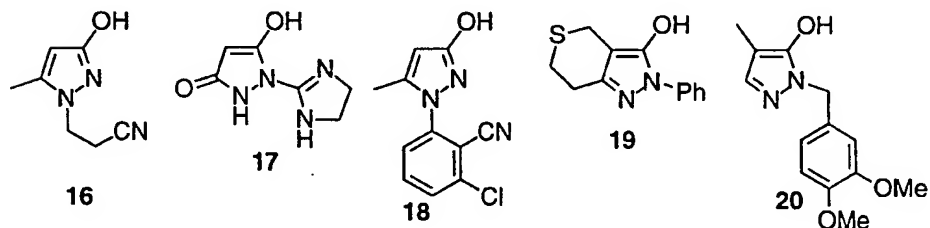
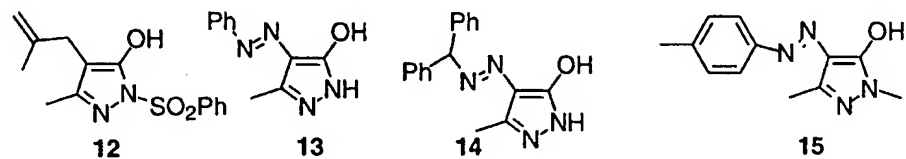
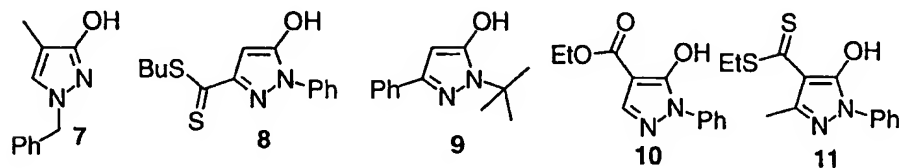
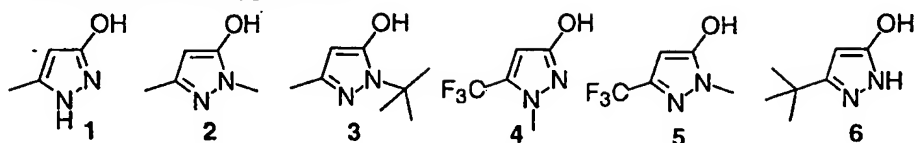
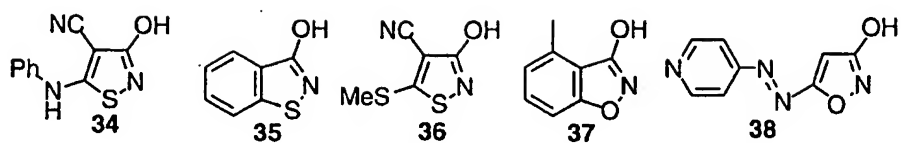
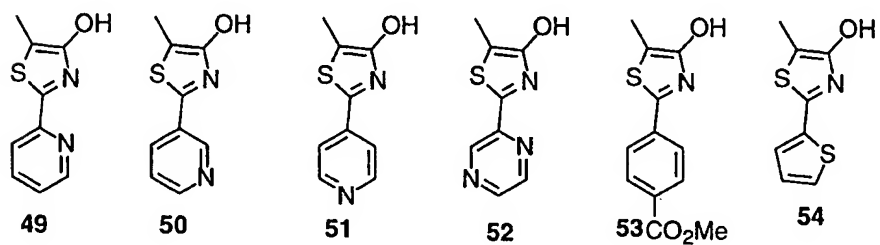
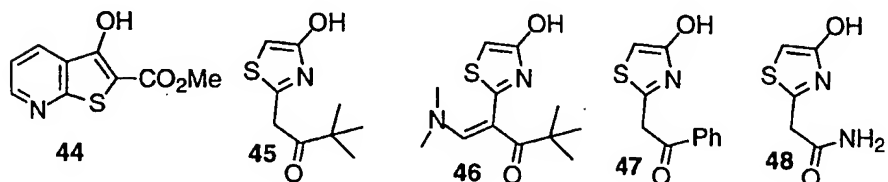
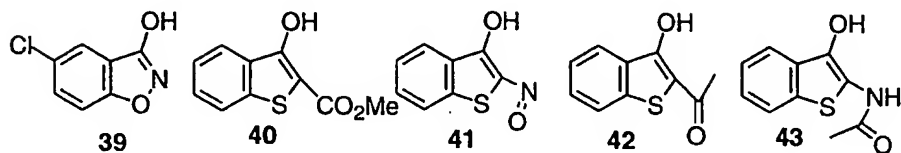


Table 15. Alcohols of the type A-OH

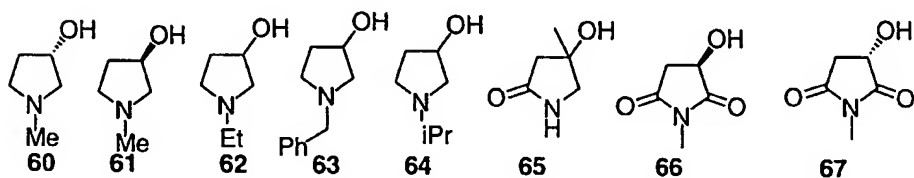
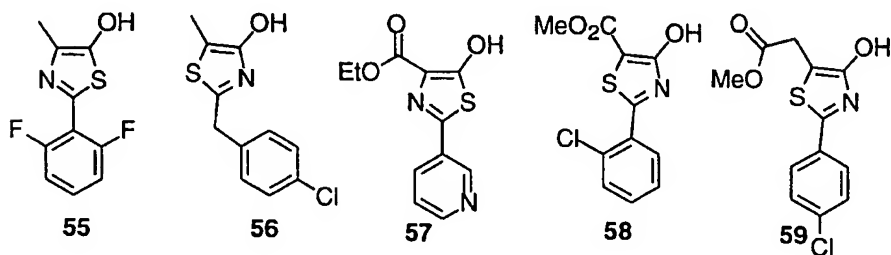




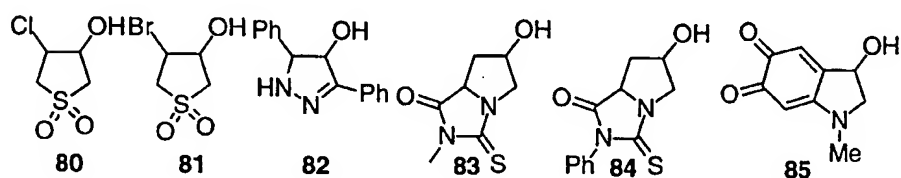
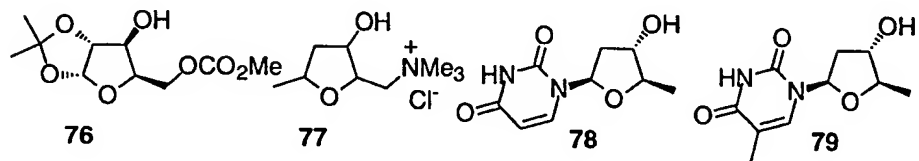
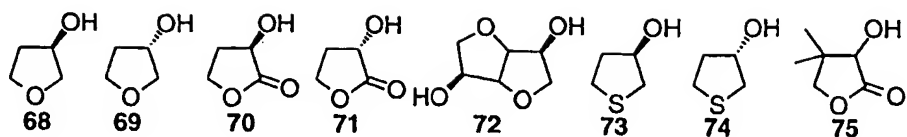
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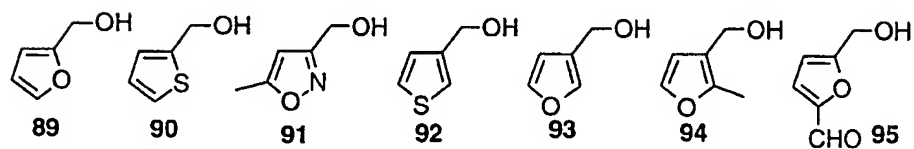
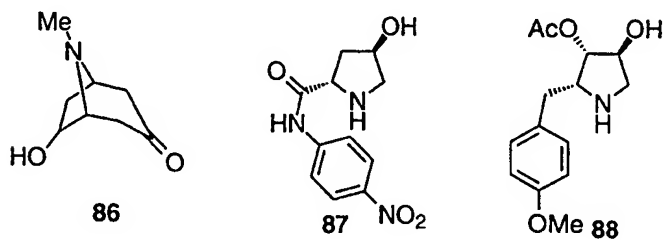
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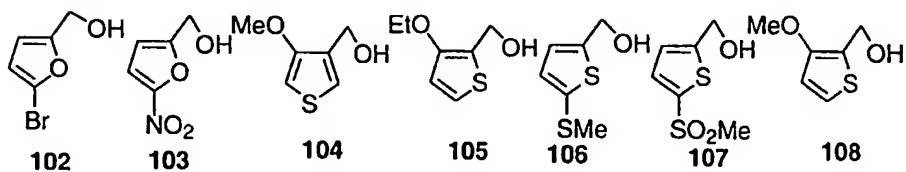
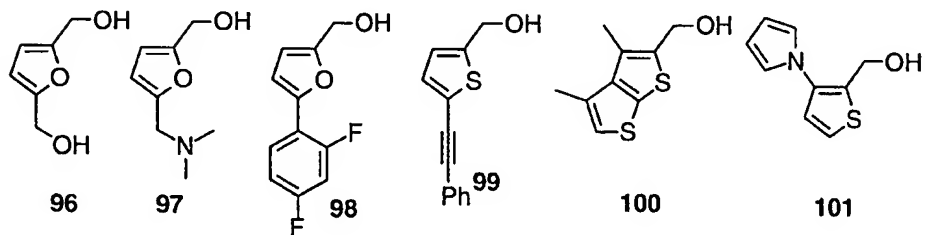
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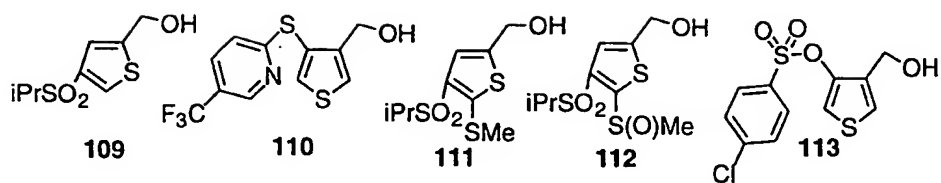


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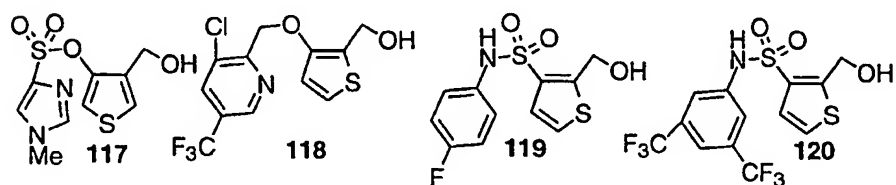
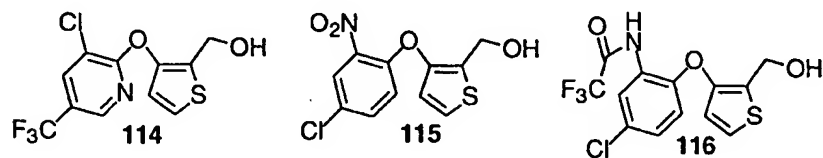


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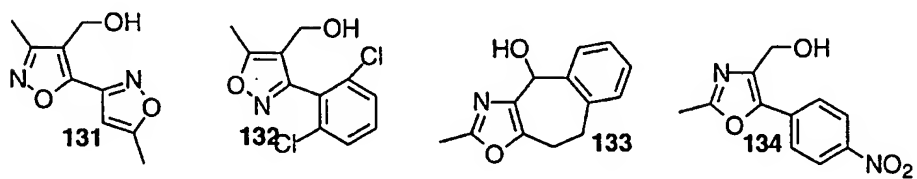
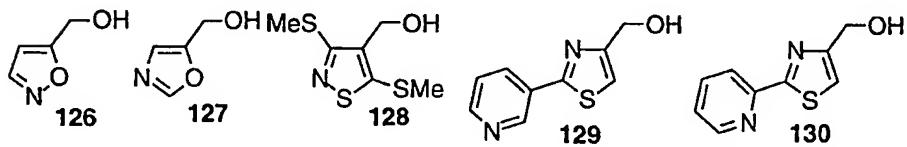
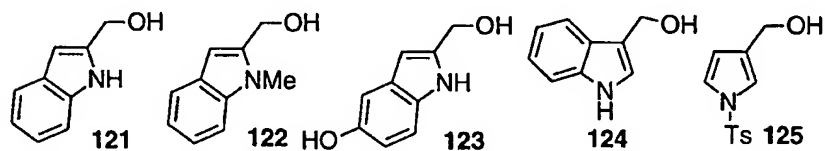




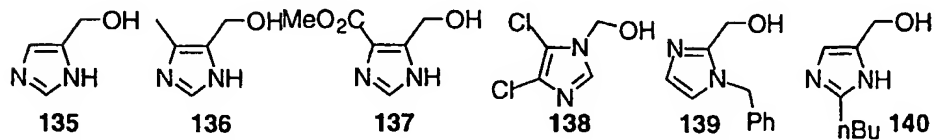
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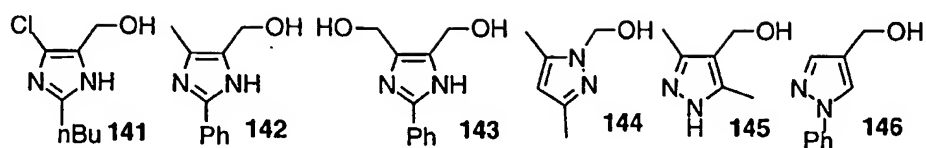


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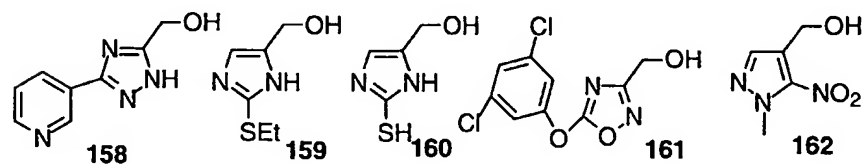
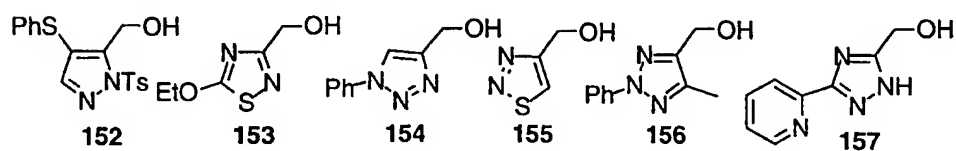
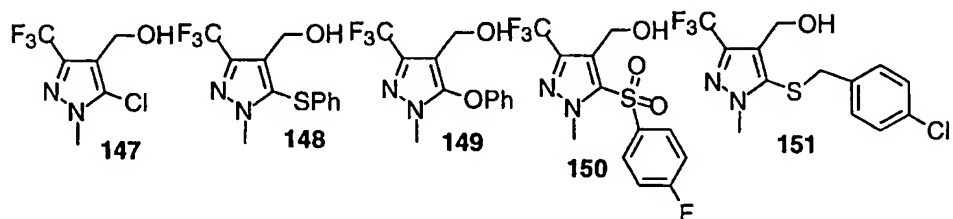


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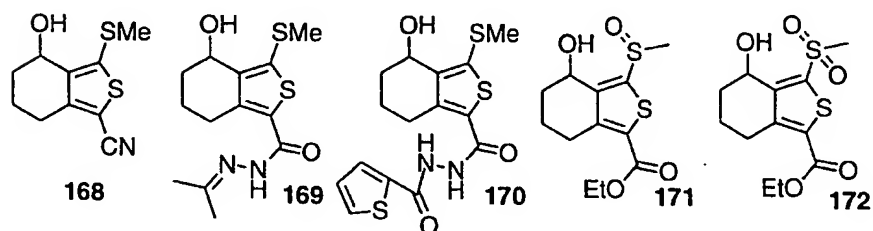
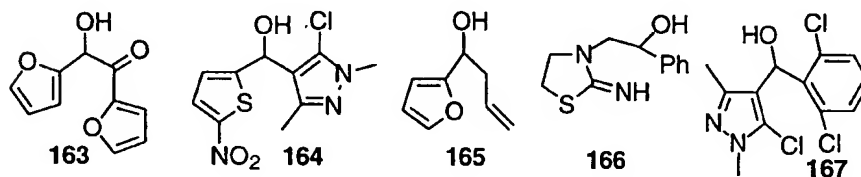




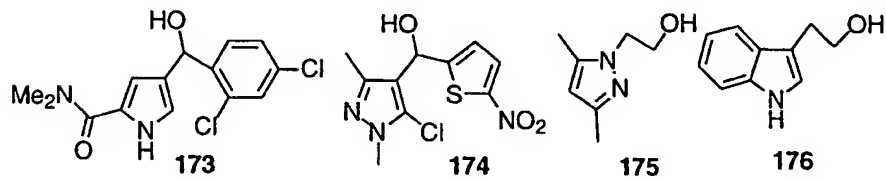
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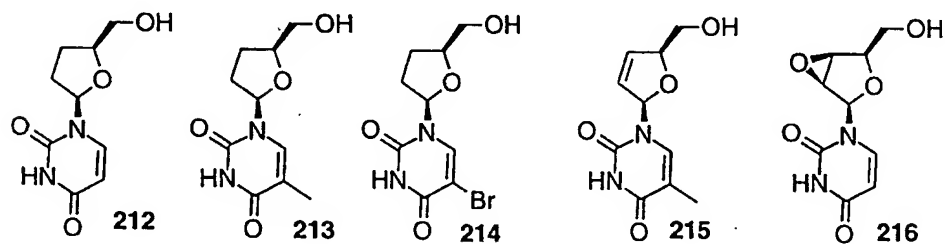
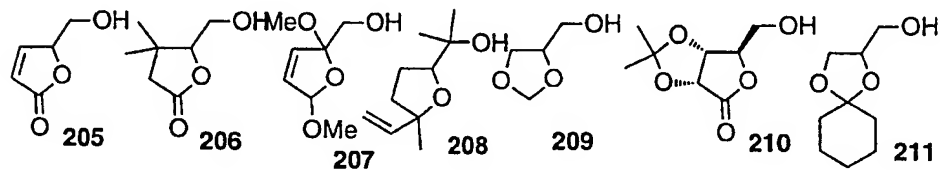
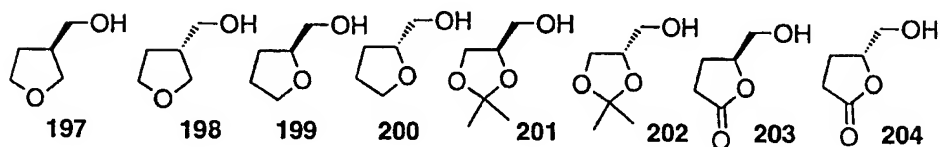
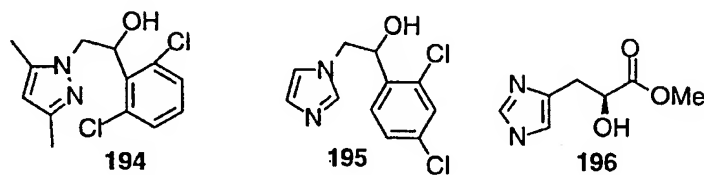
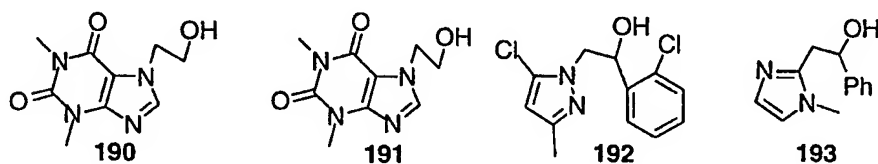
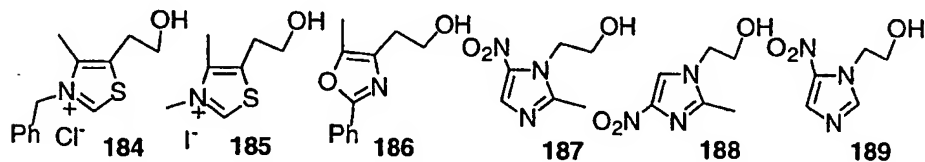
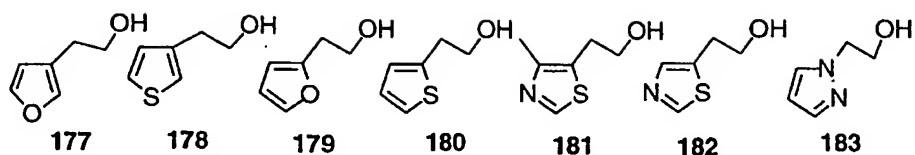


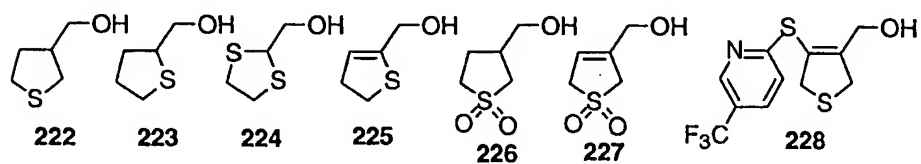
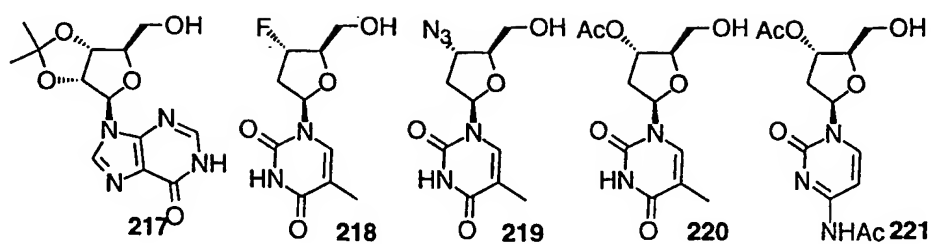
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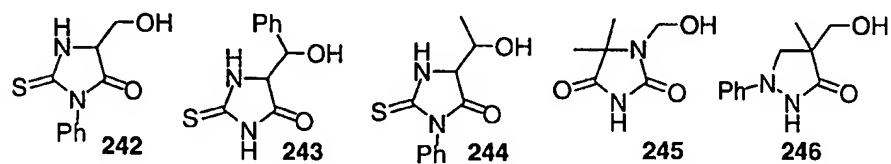
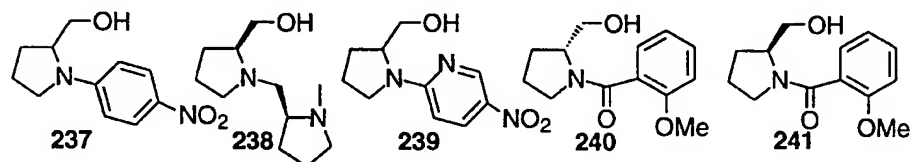
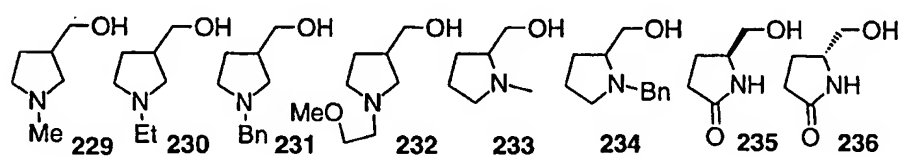
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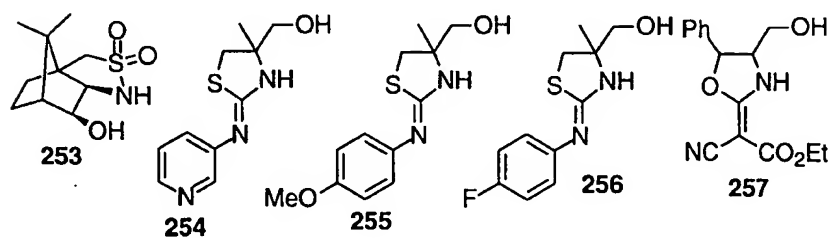
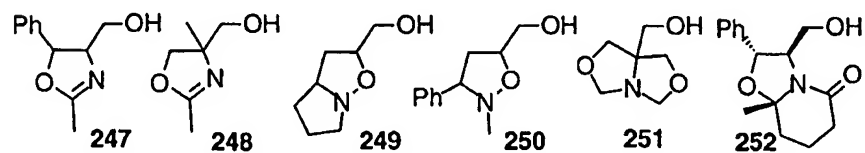




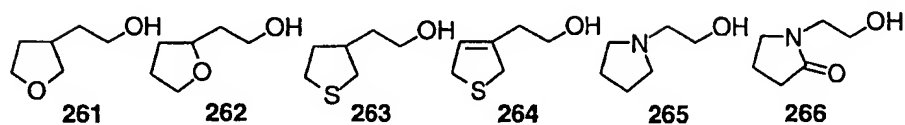
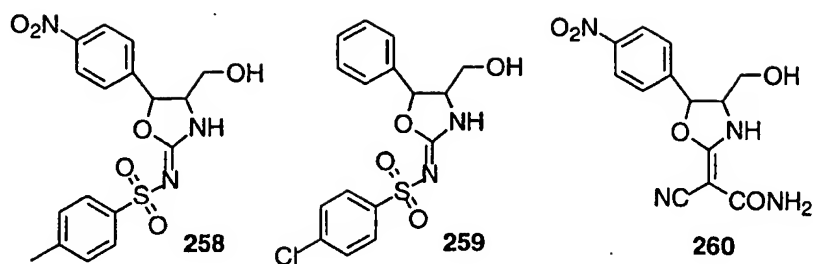
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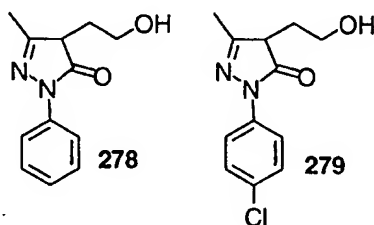
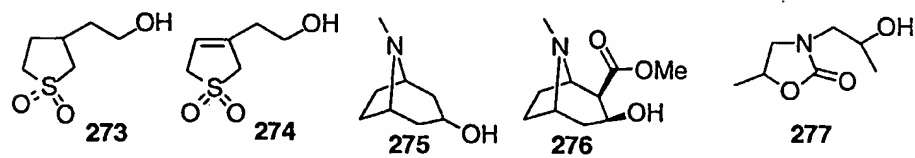
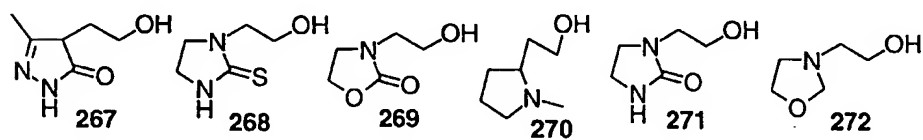
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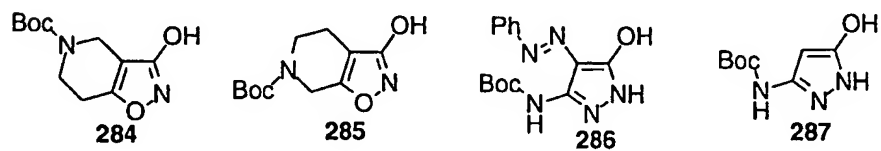
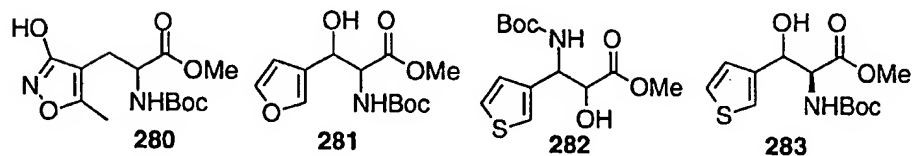
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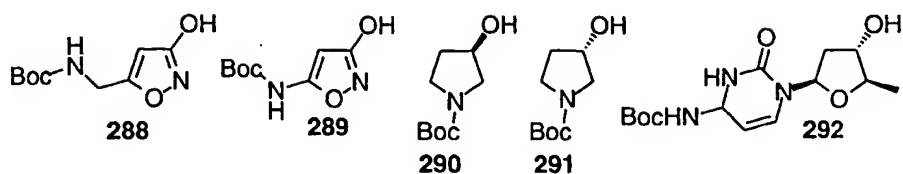


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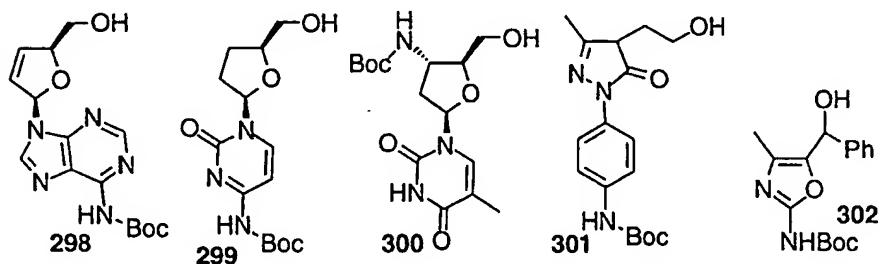
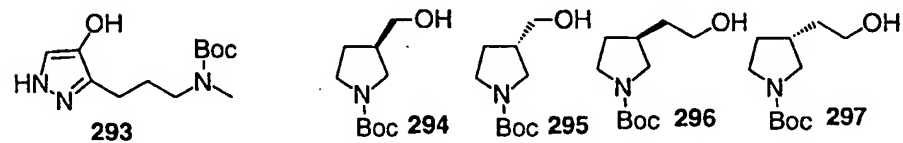


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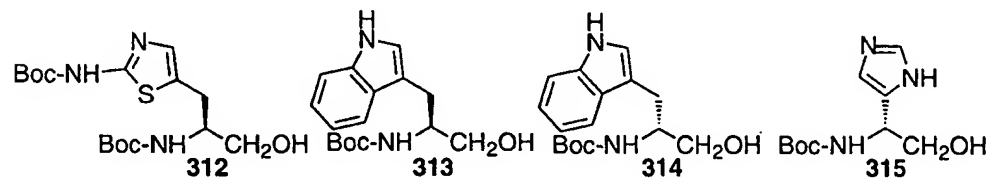
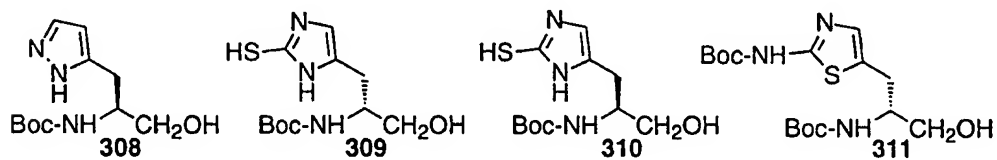
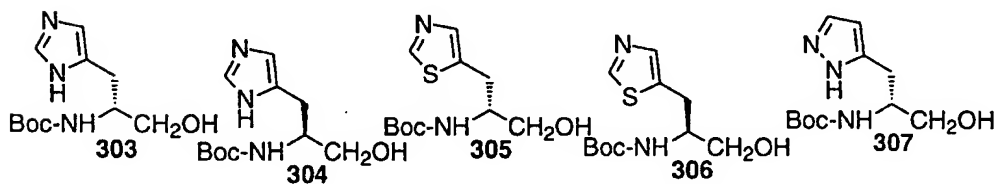




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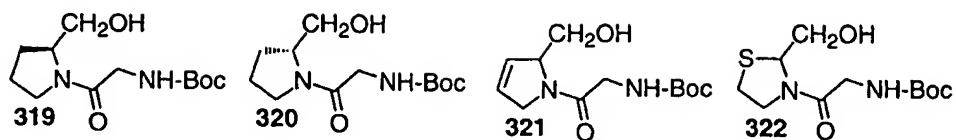


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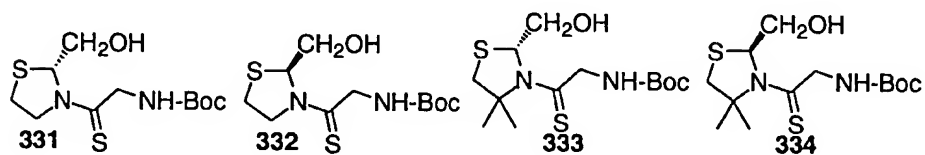
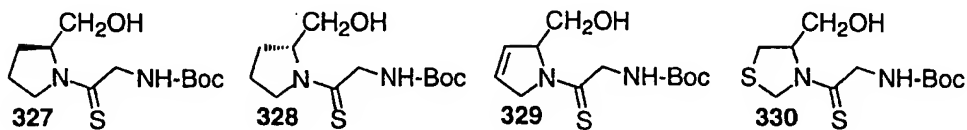
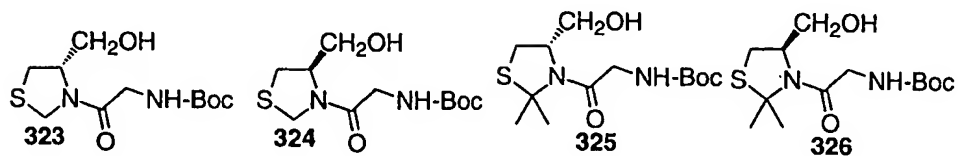


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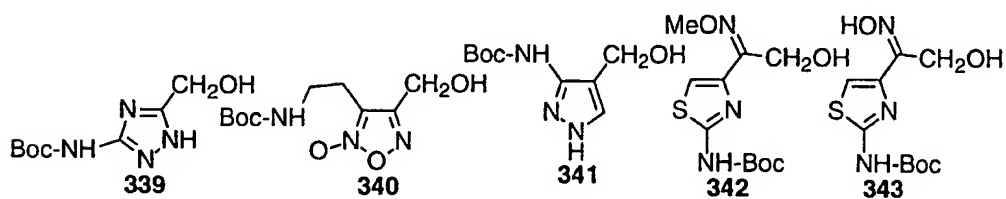
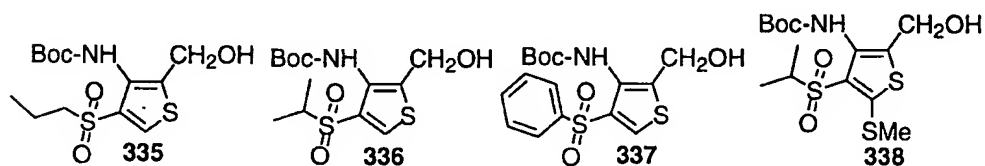




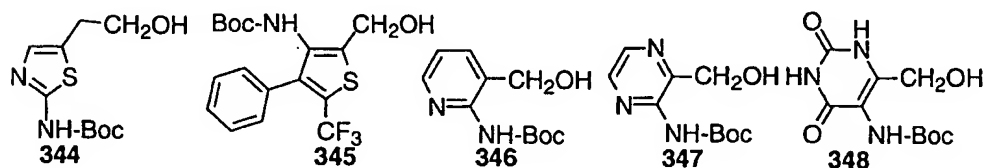
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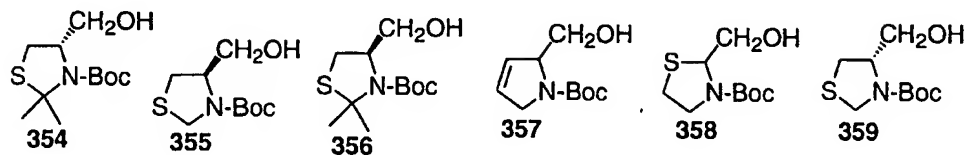
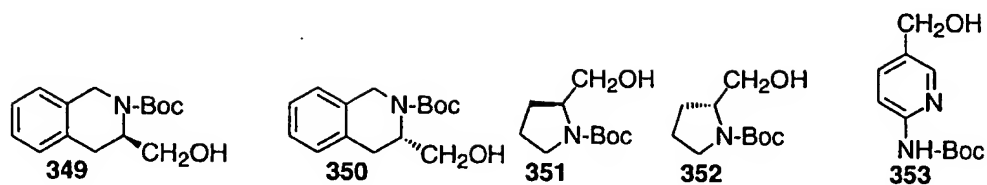


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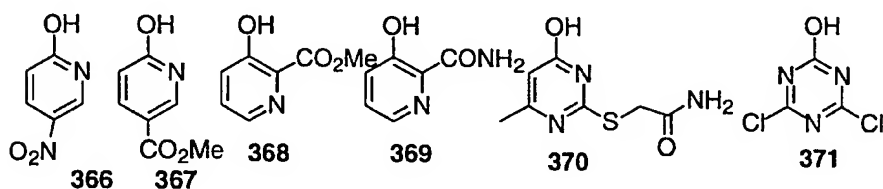
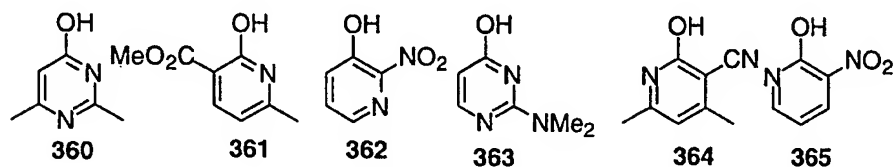


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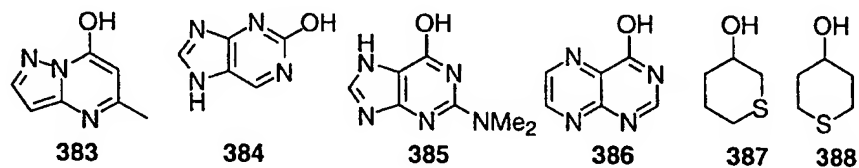
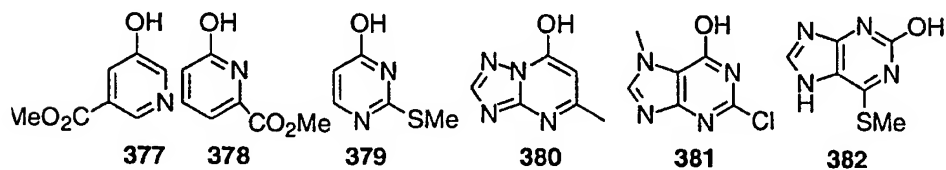
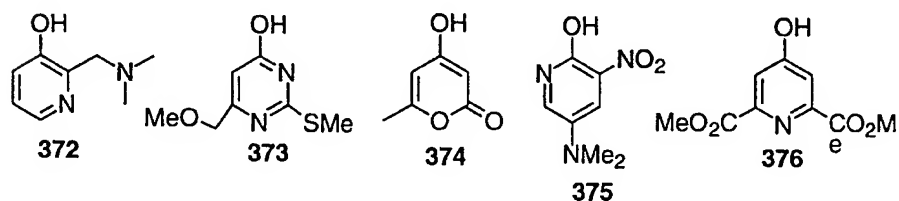




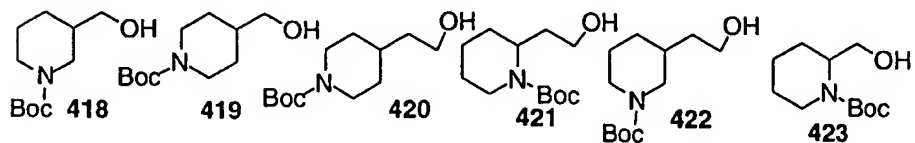
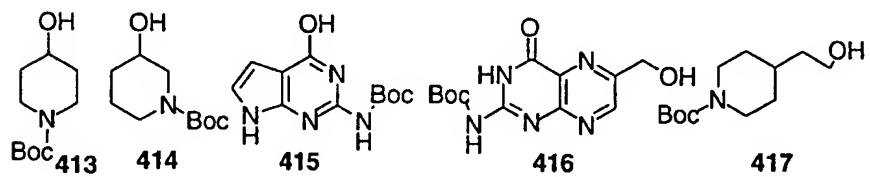
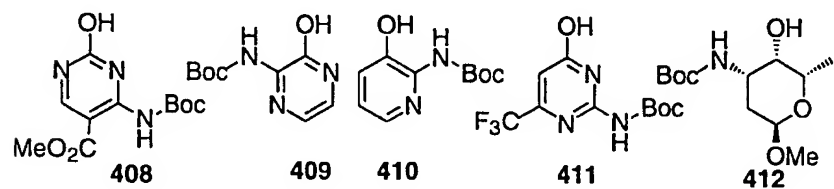
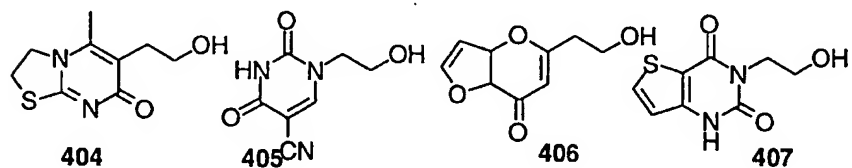
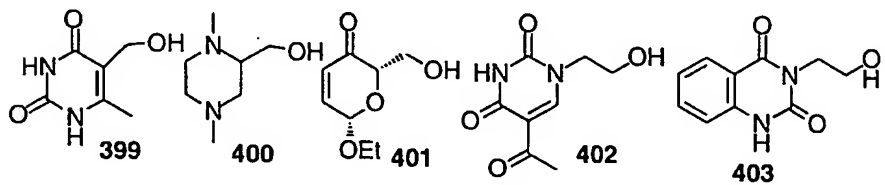
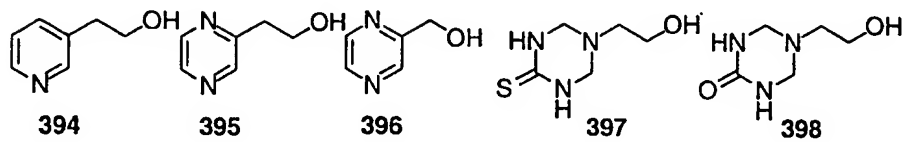
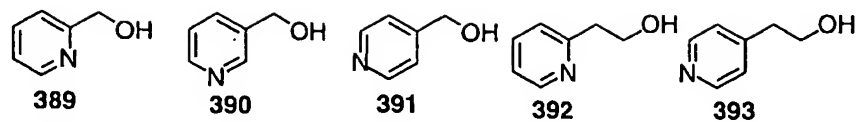
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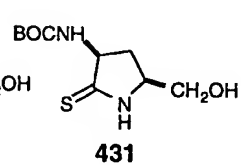
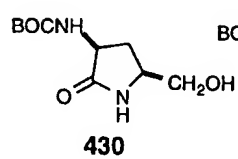
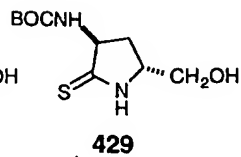
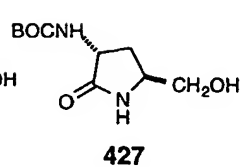
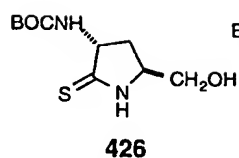
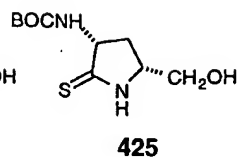
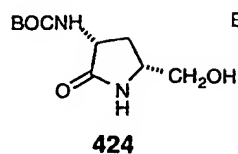
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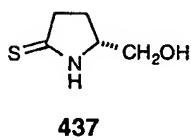
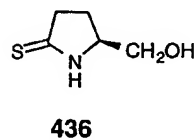
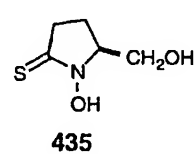
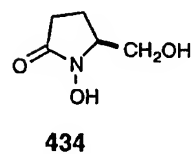
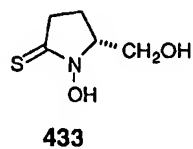
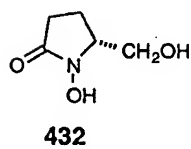
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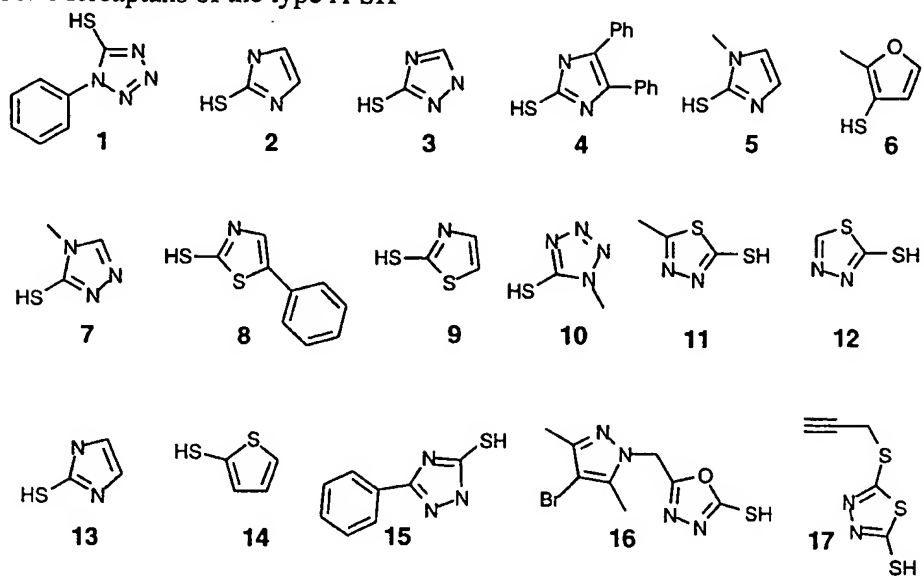
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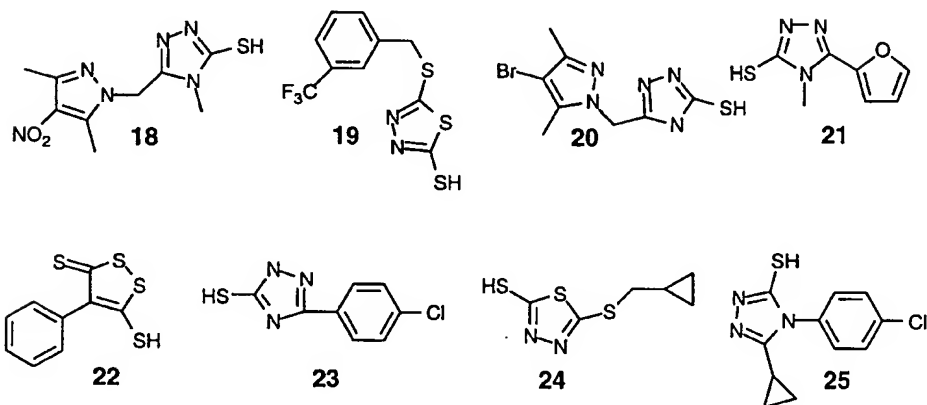
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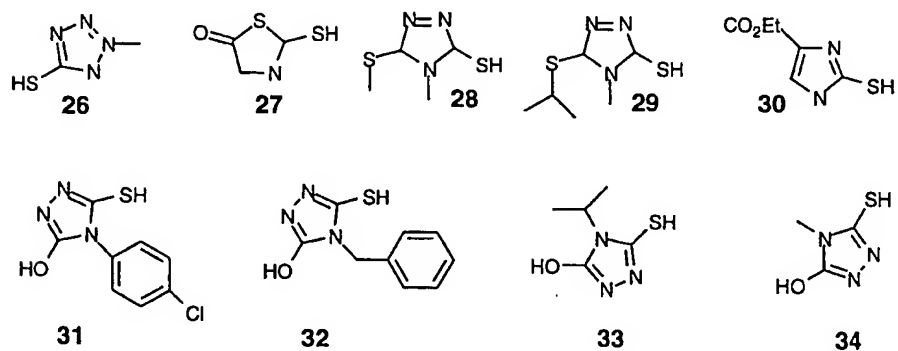
3205 Table 16. Mercaptans of the type A-SH



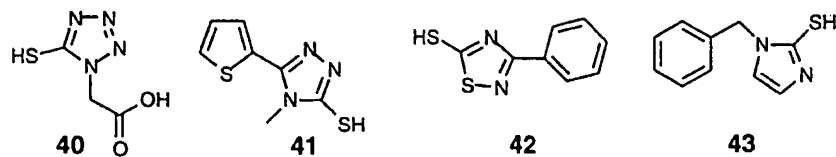
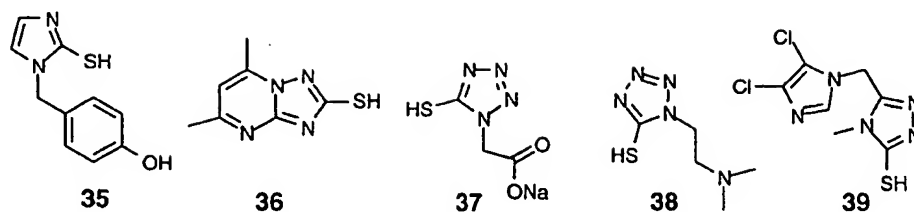
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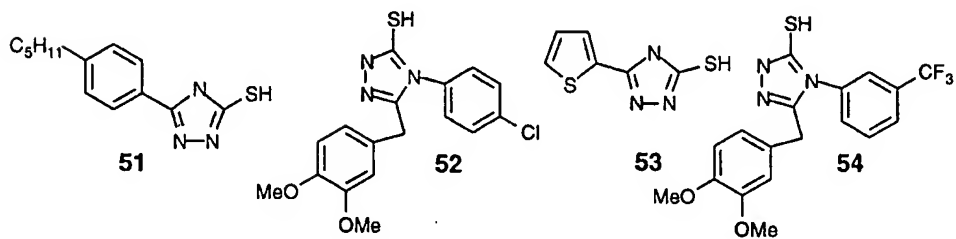
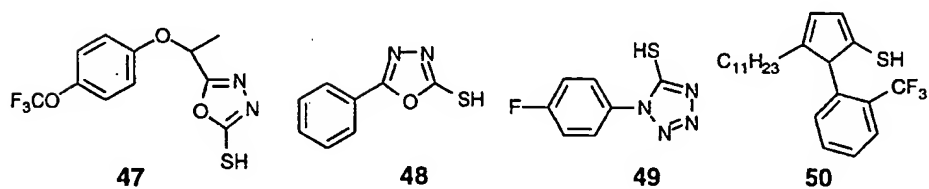
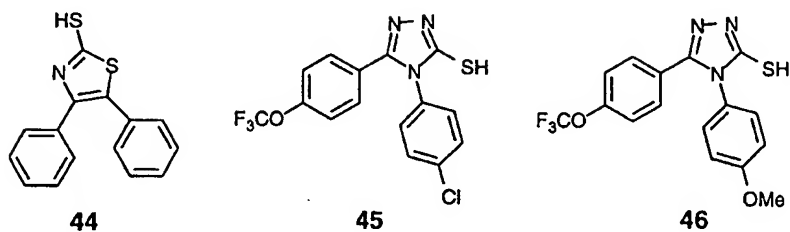
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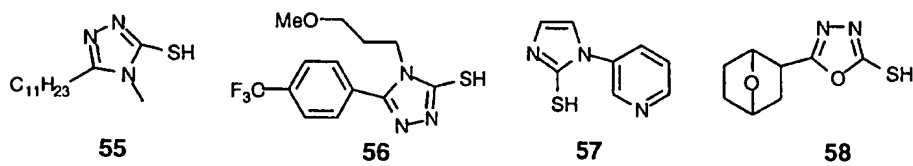
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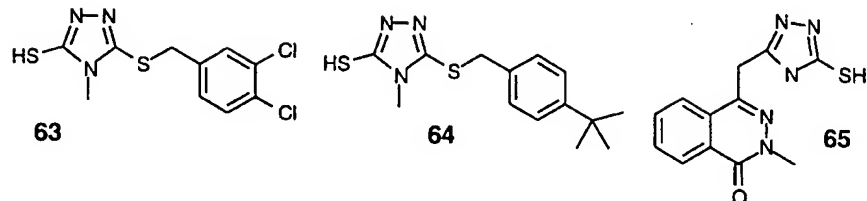
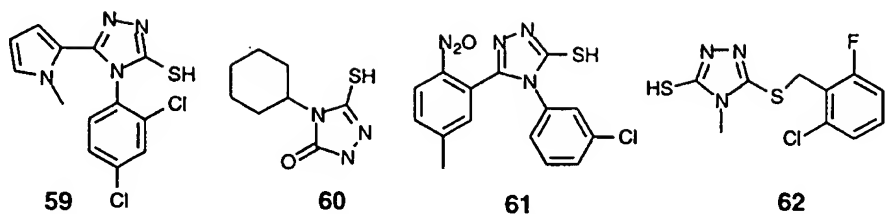


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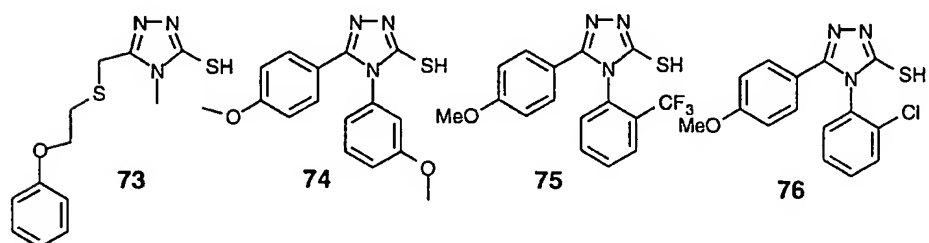
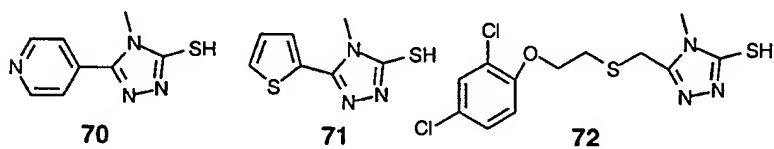
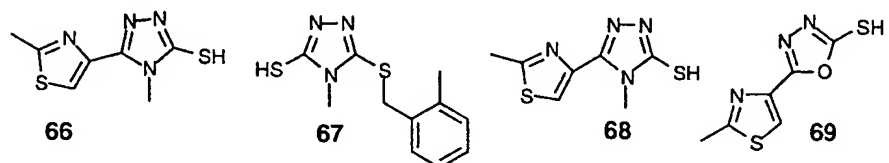


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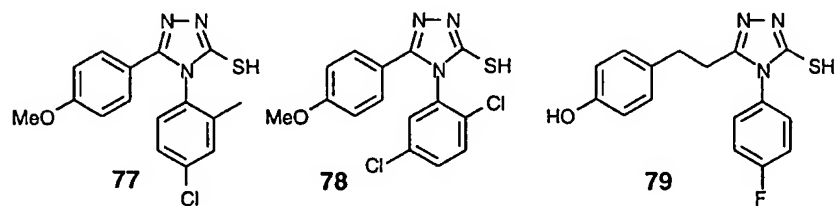


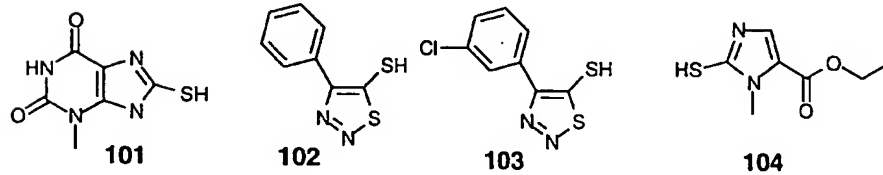
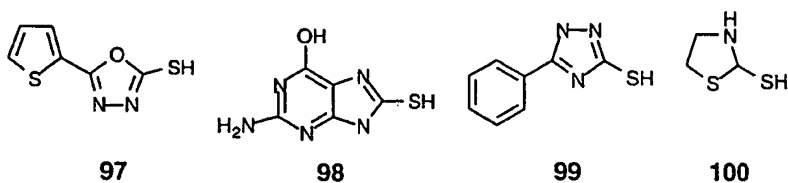
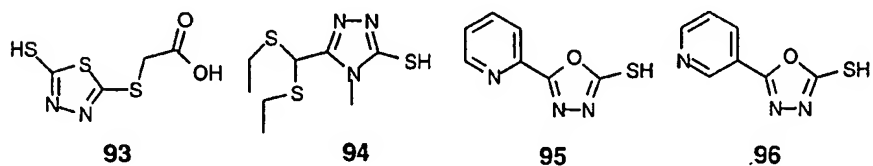
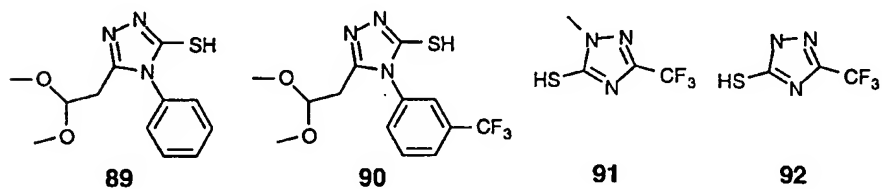
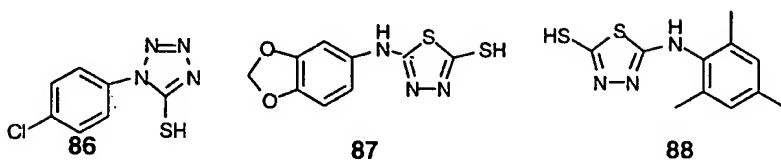
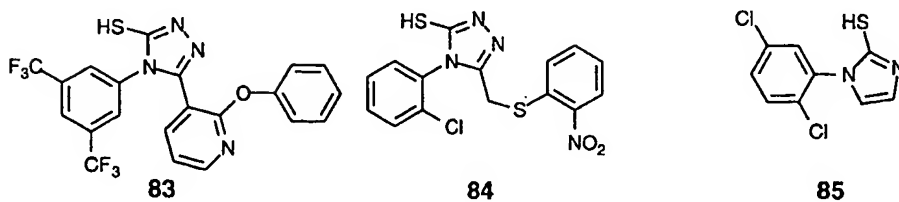
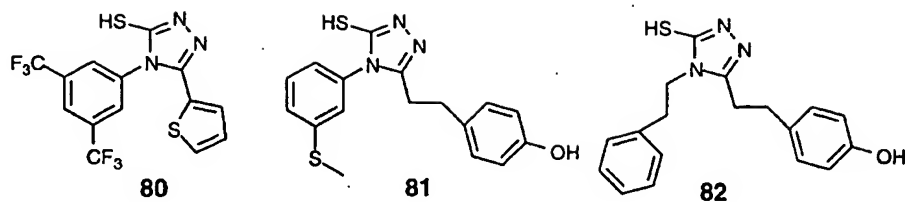


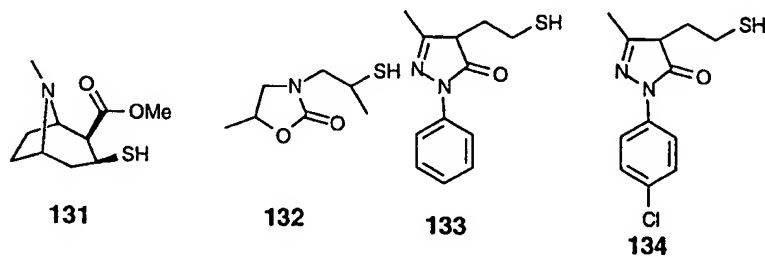
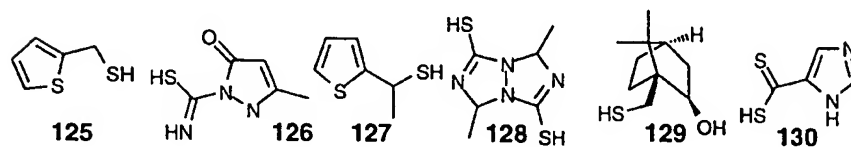
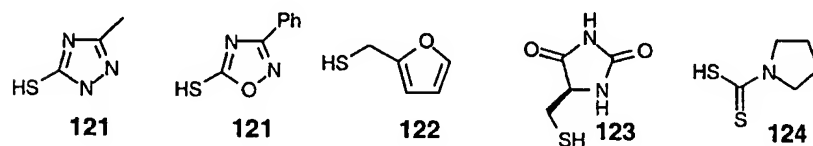
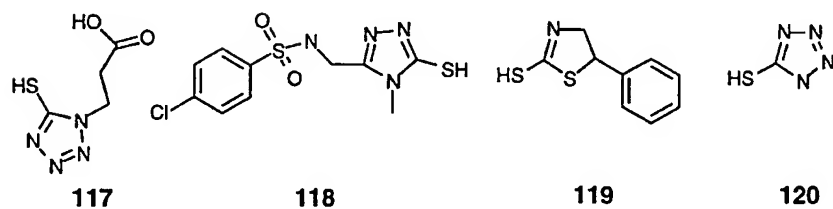
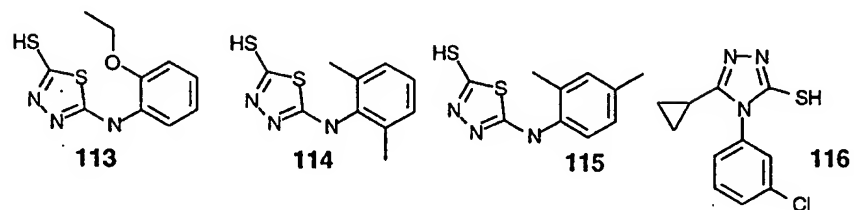
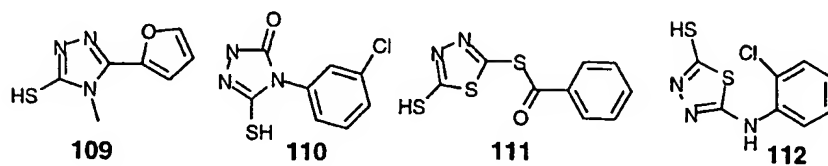
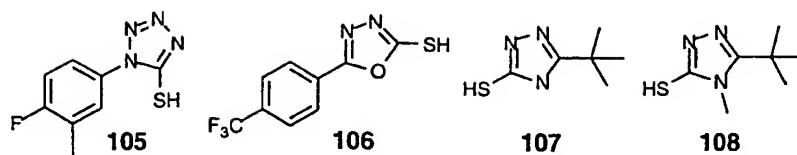
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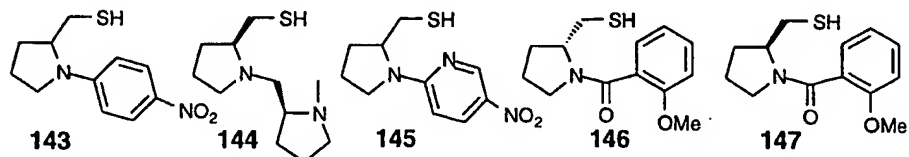
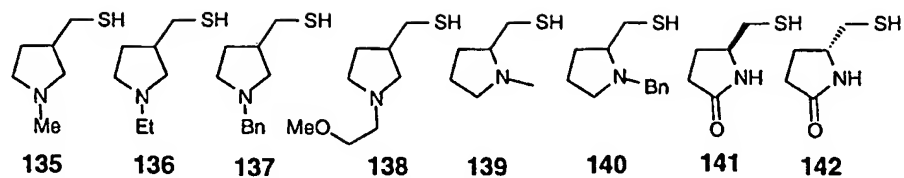


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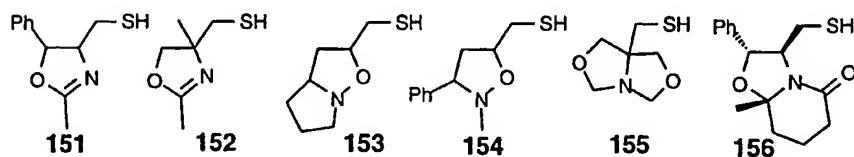
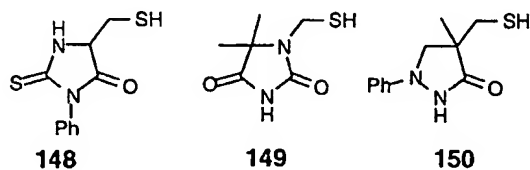




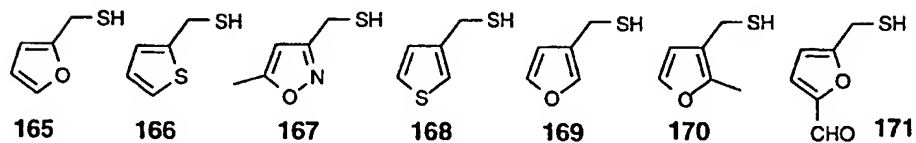
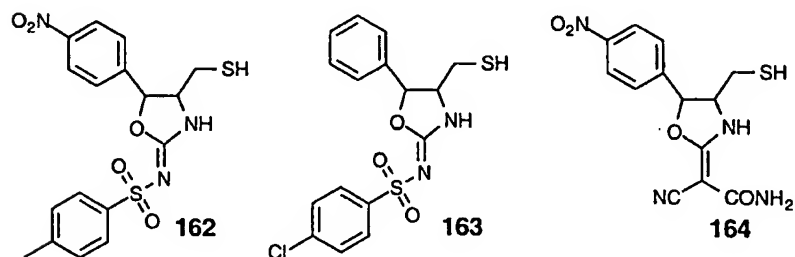
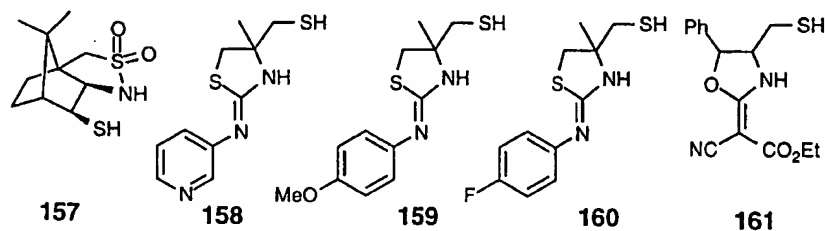




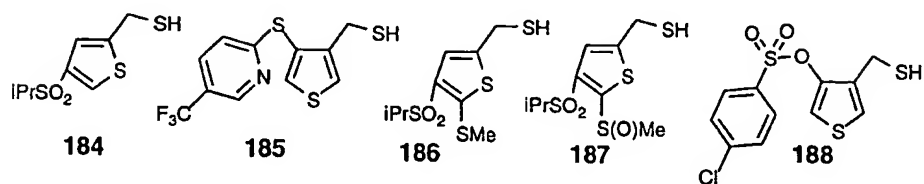
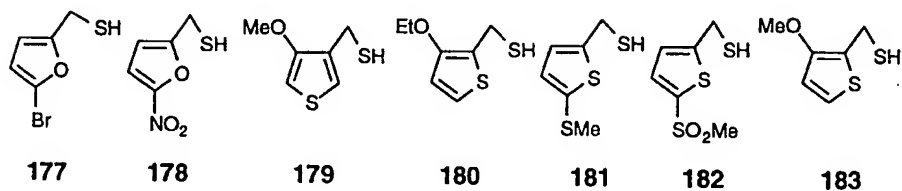
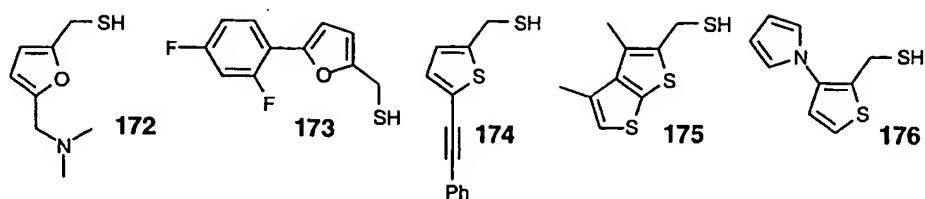
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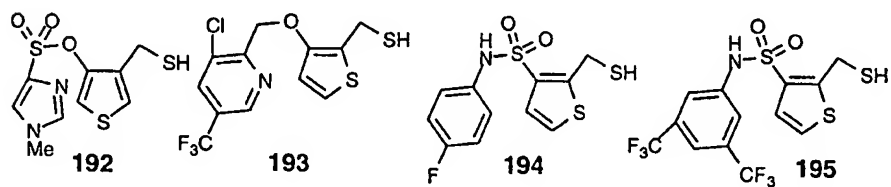
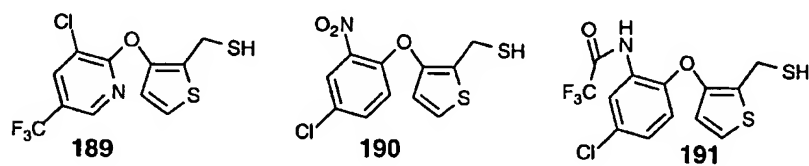
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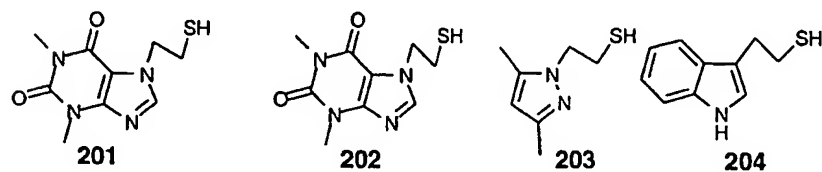
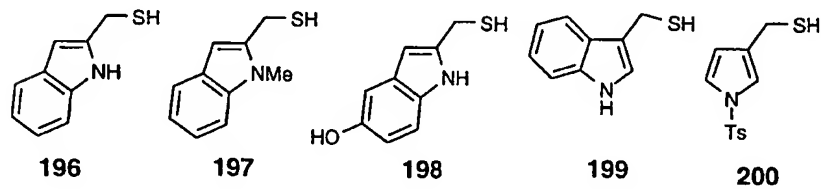
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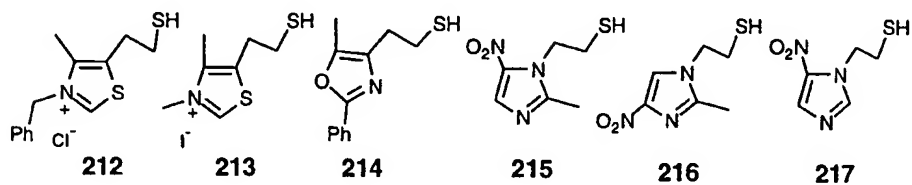
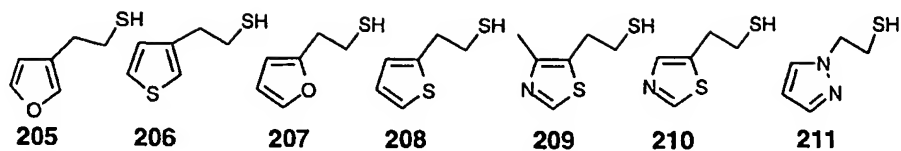
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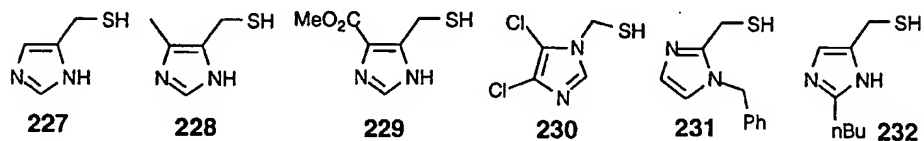
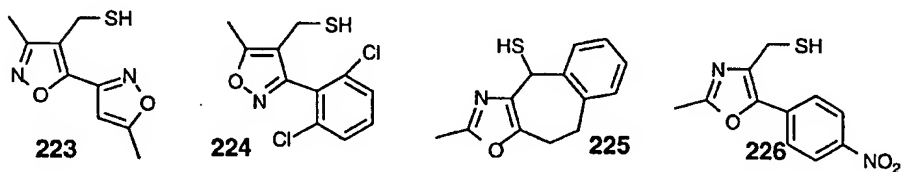
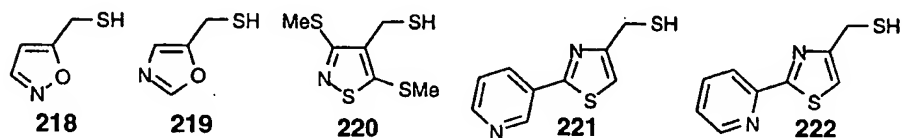
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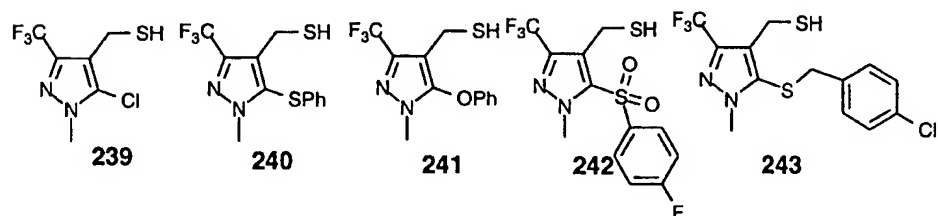
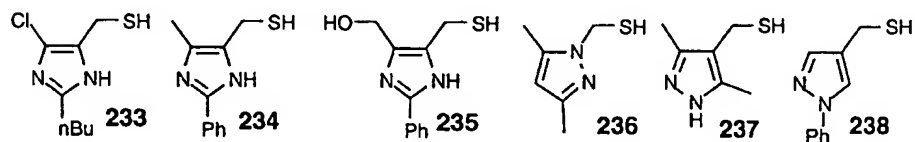
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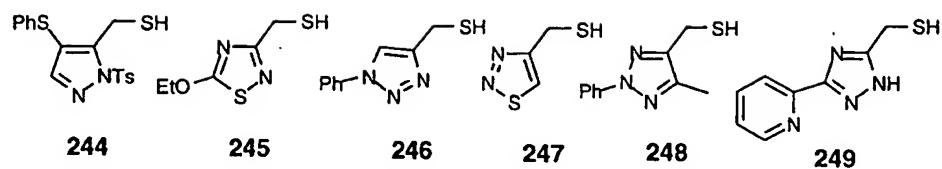


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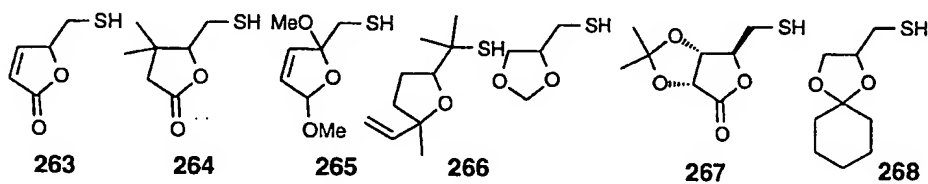
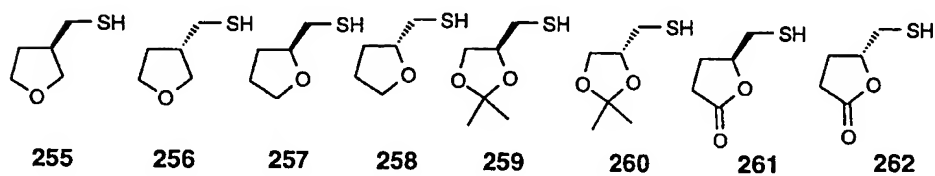
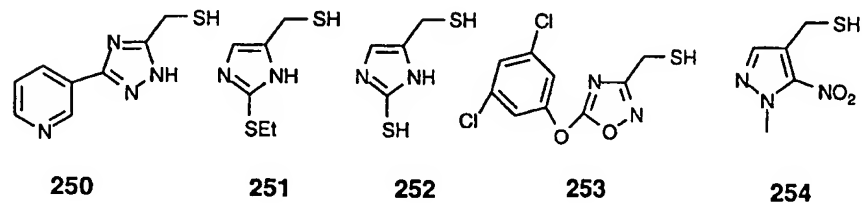


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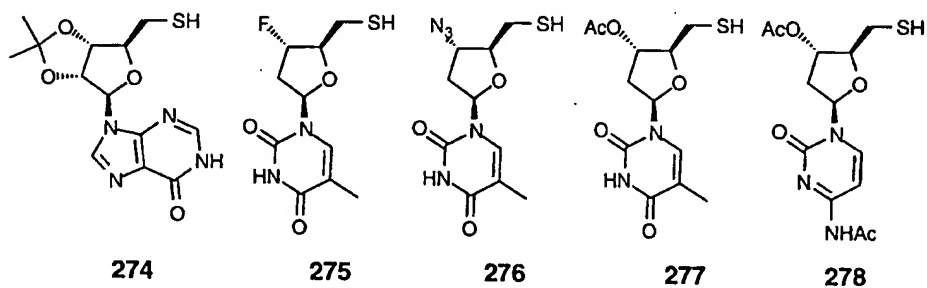
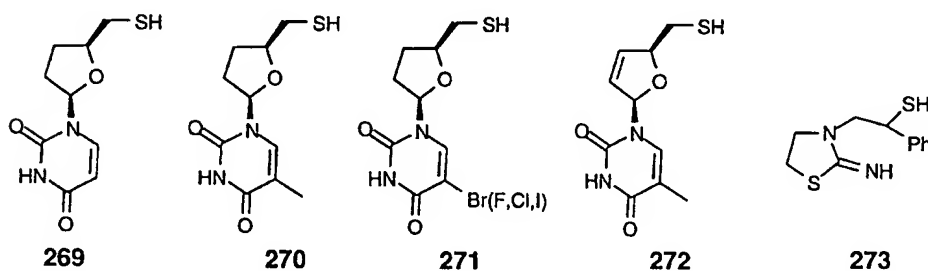




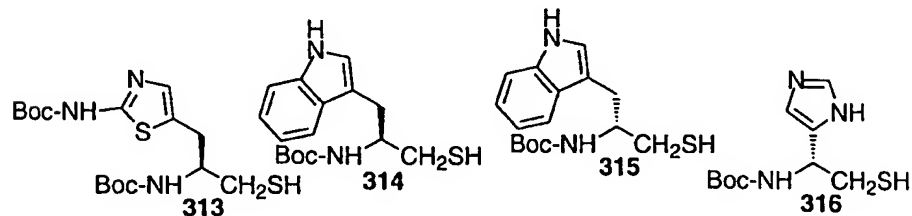
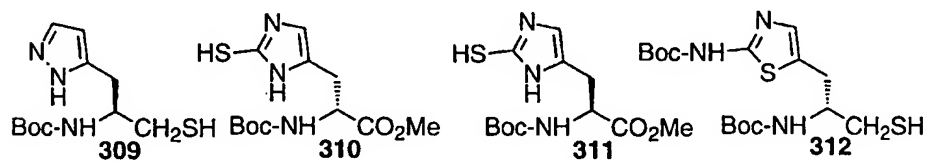
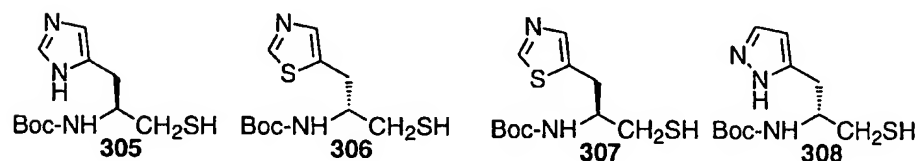
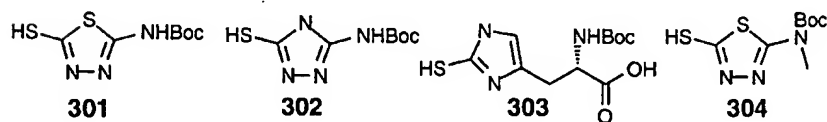
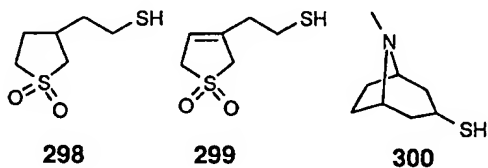
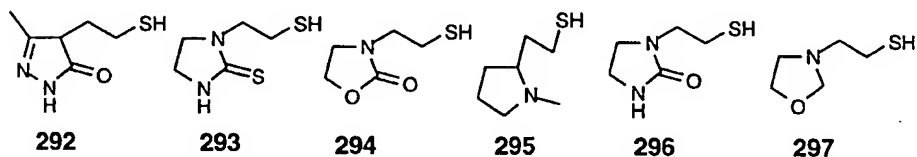
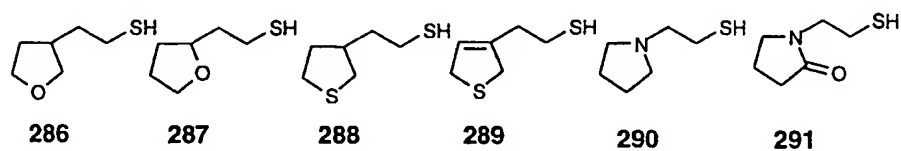
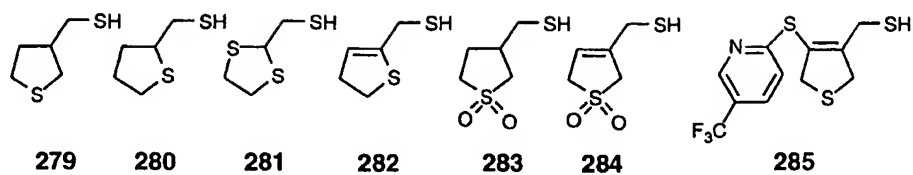
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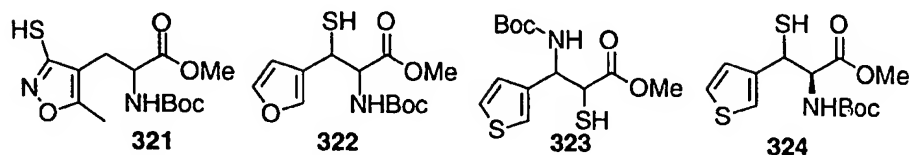
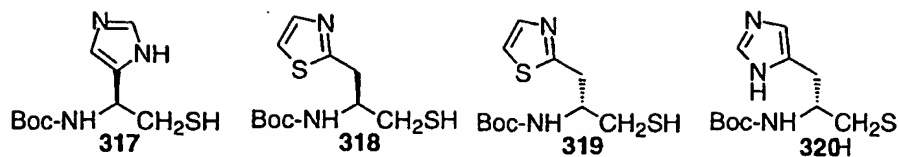


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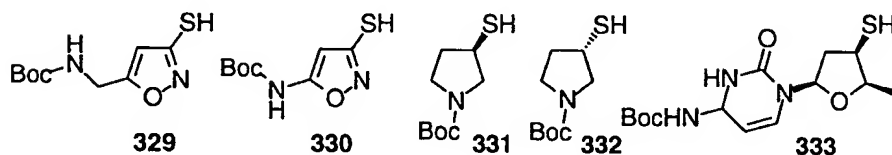
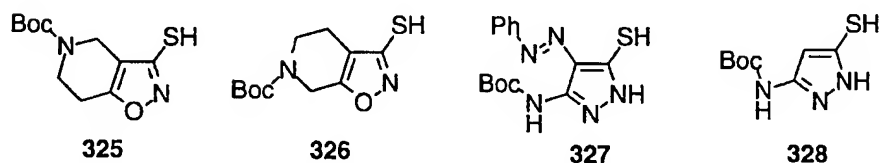


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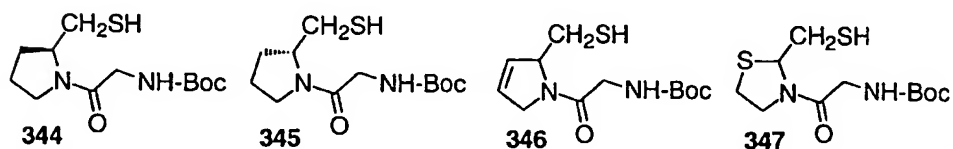
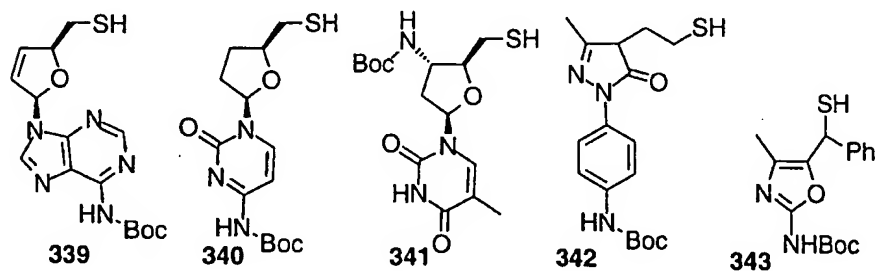
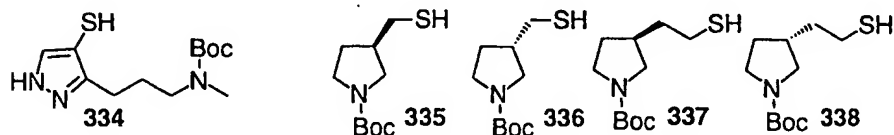




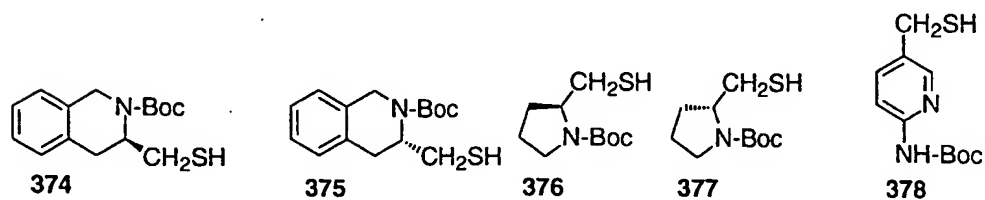
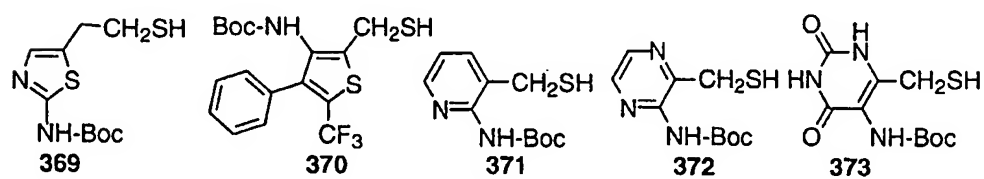
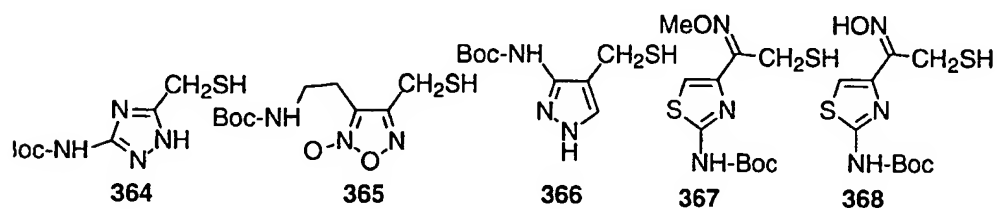
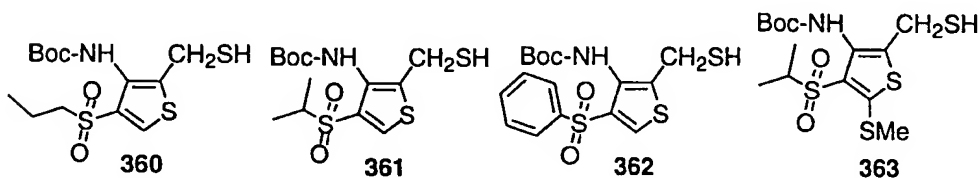
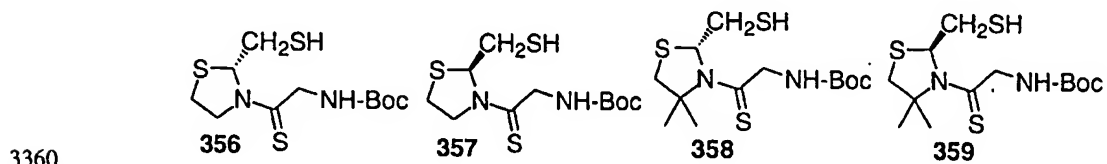
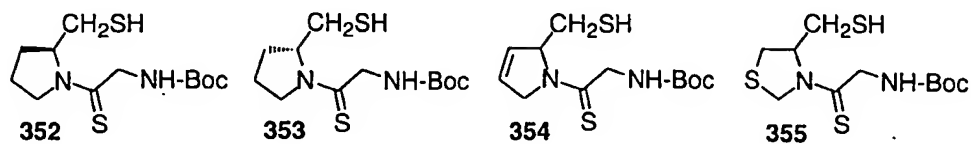
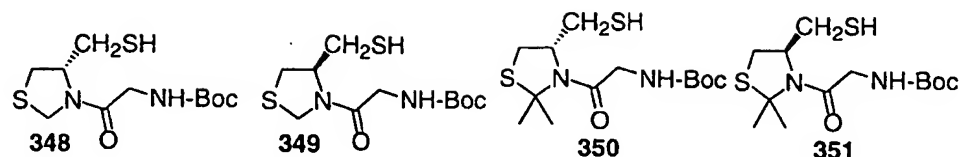
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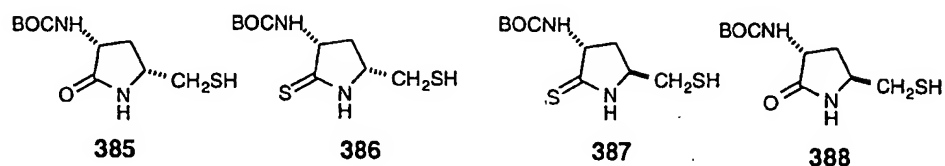
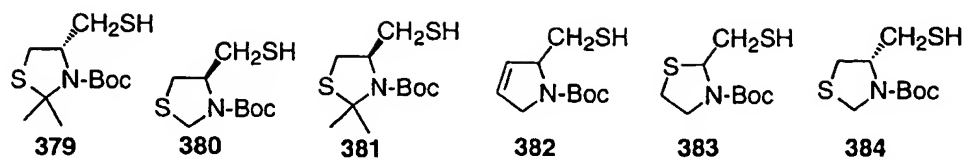
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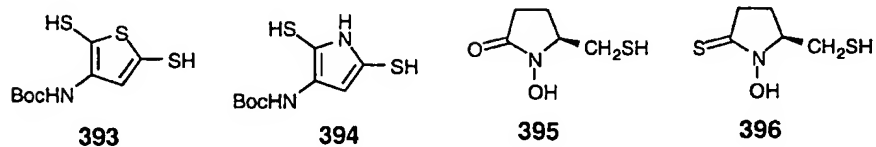
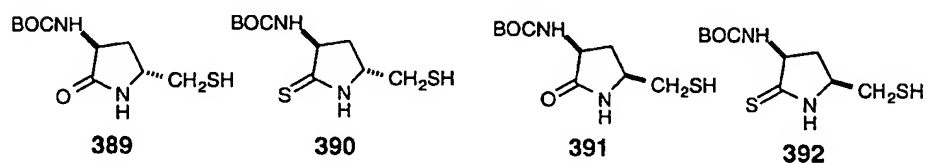
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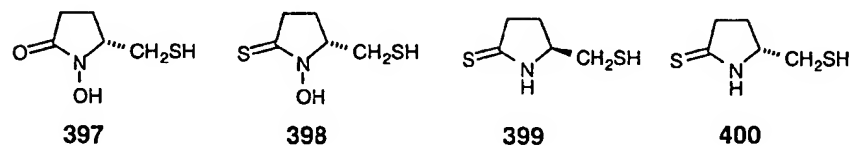
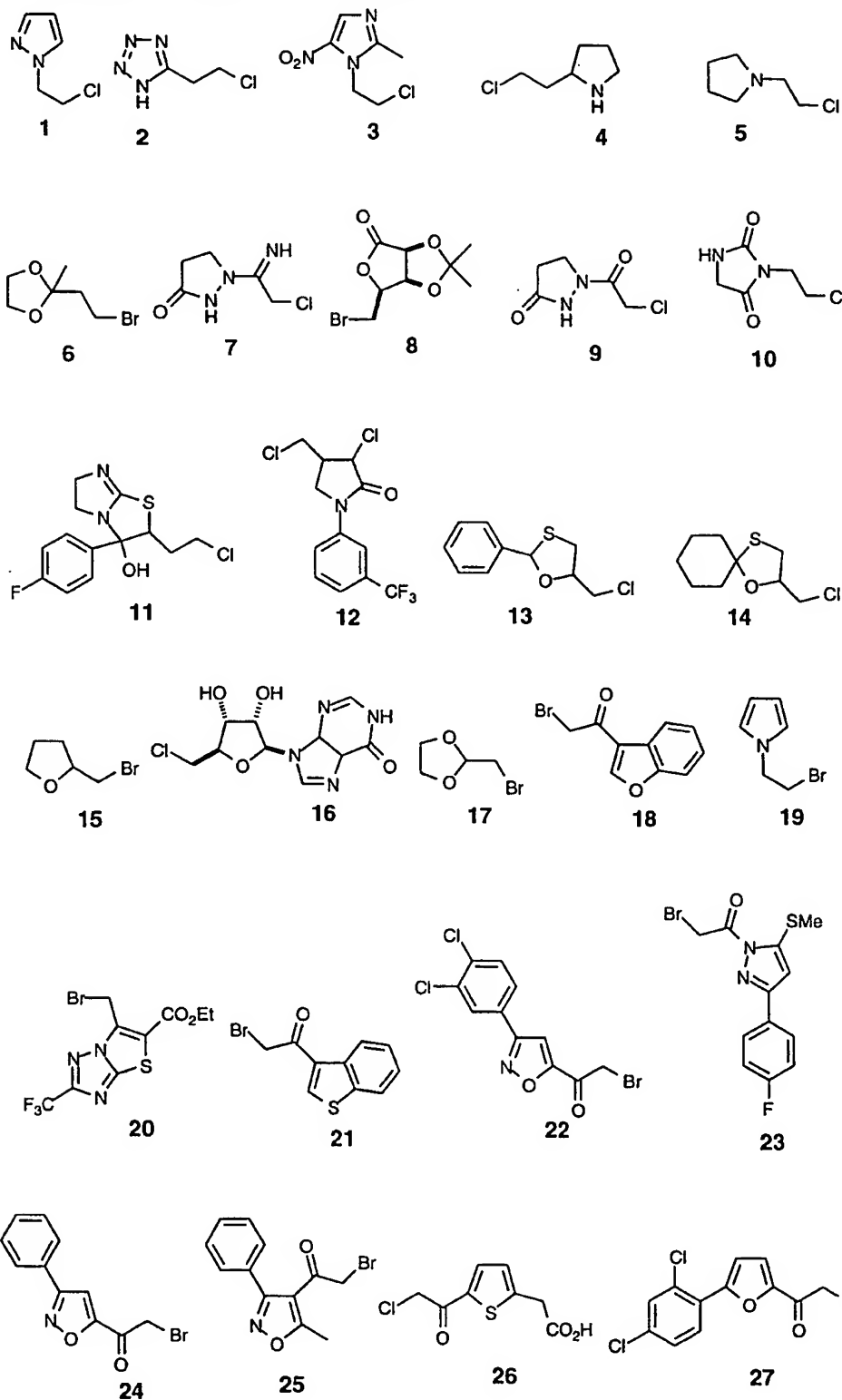
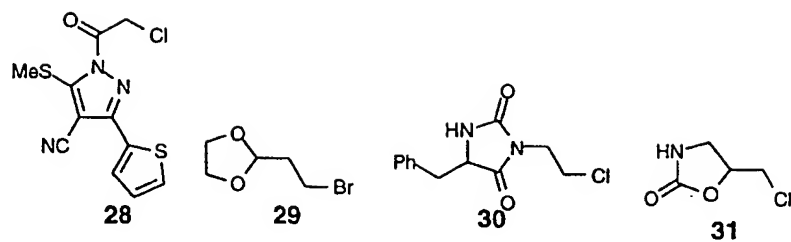


Table 17. Halides of the type A-Cl, A-Br, and A-I

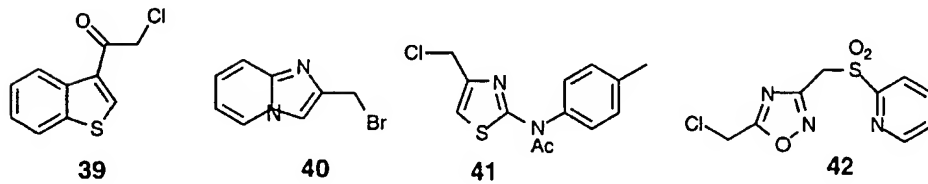
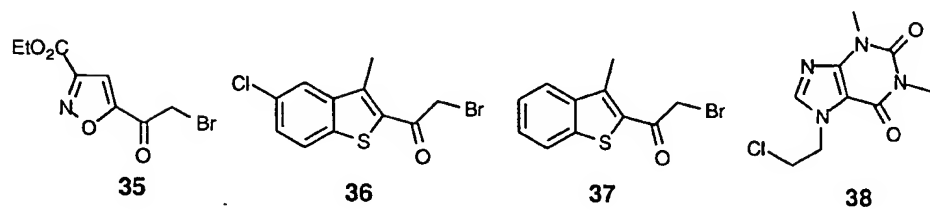
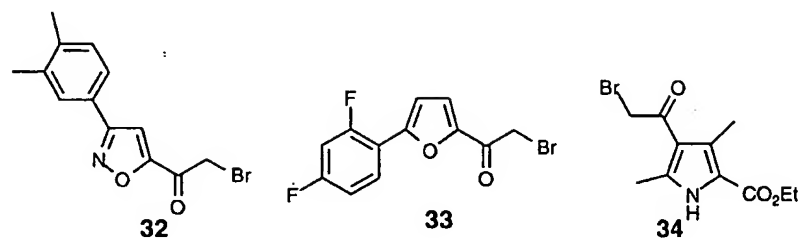


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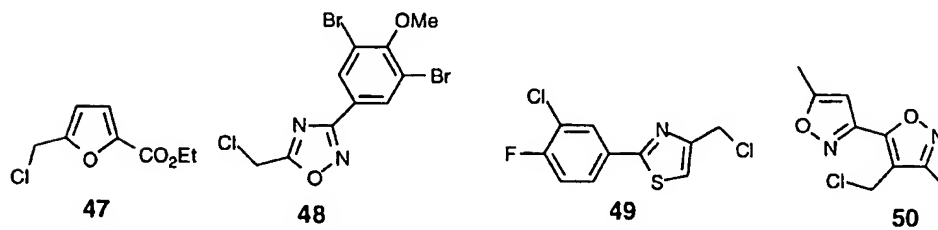
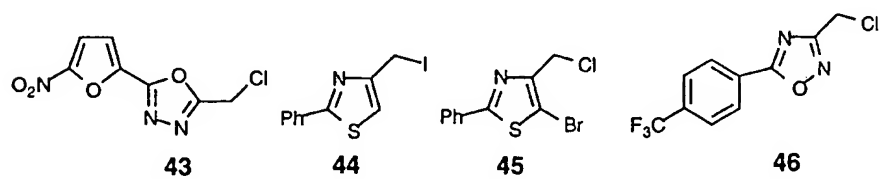
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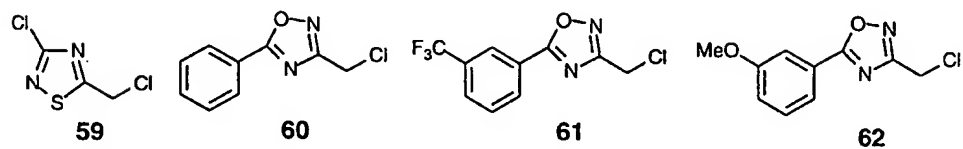
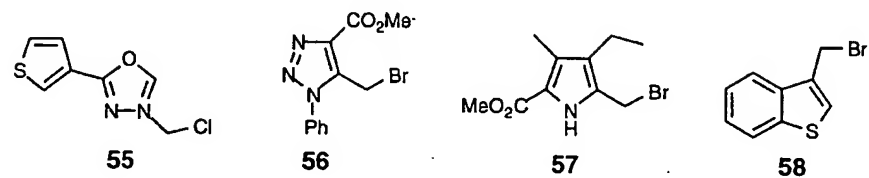
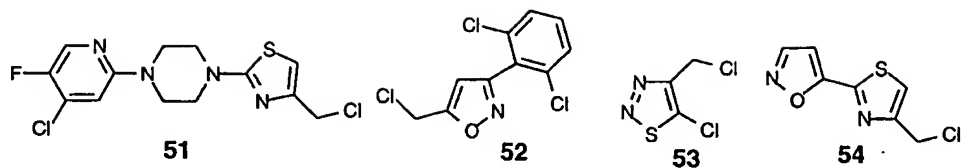
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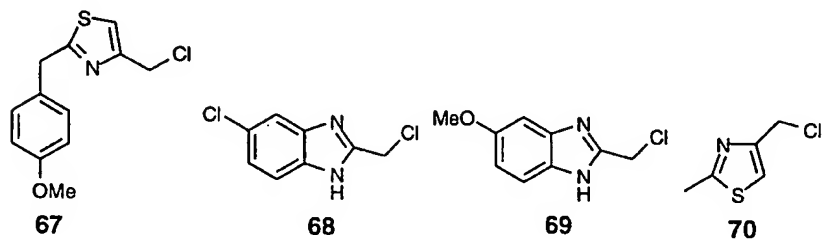
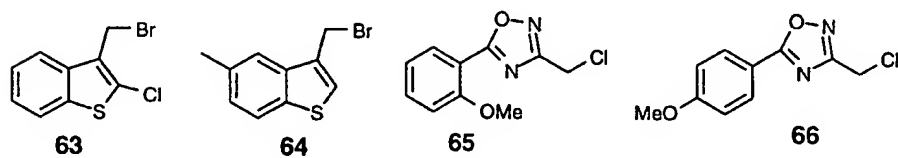
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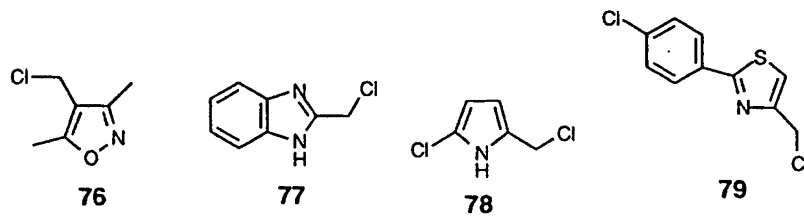
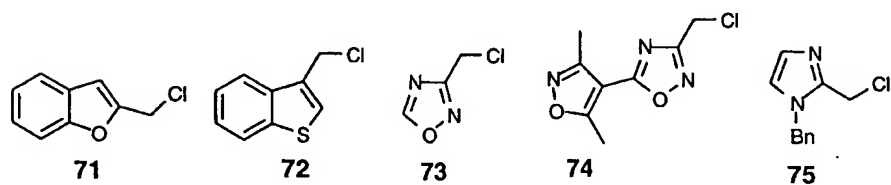
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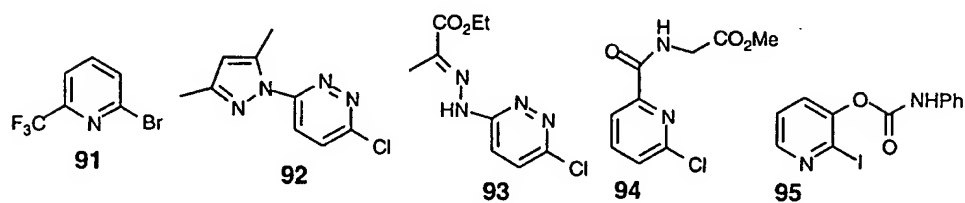
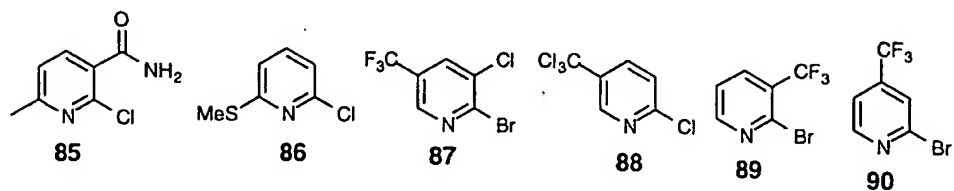
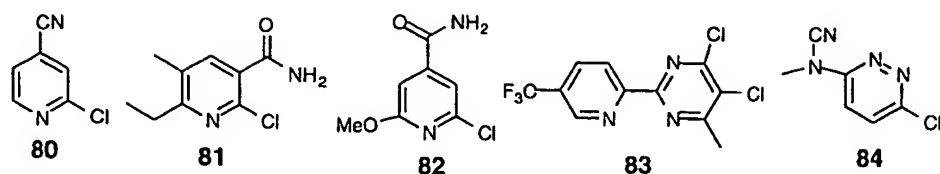
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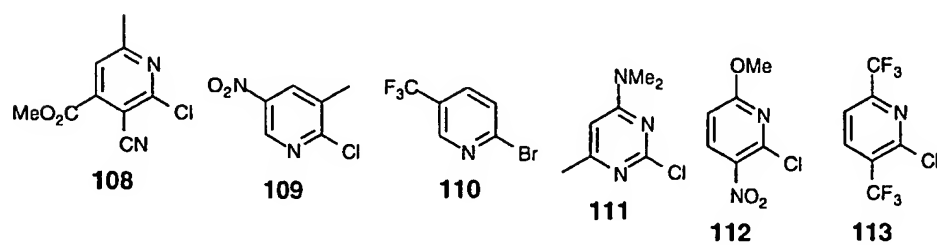
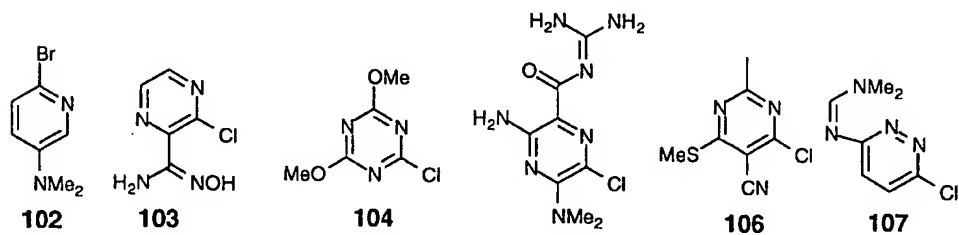
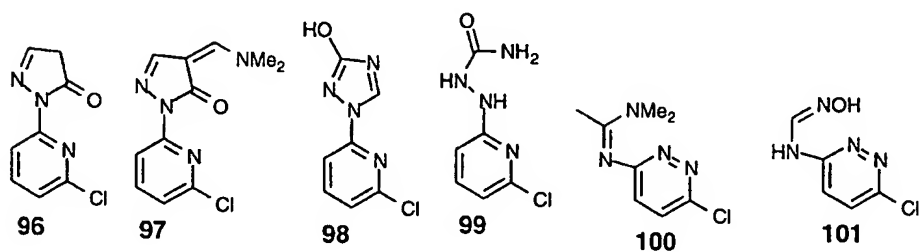
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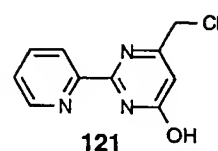
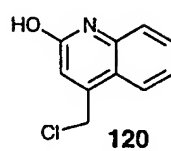
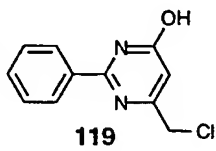
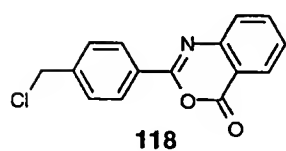
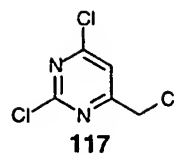
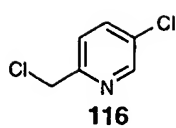
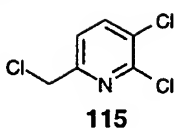
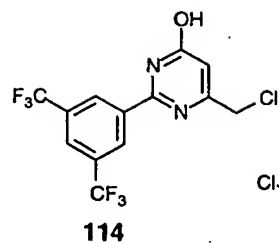
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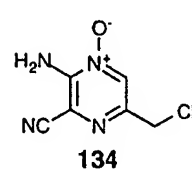
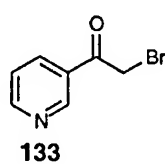
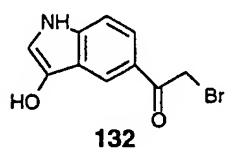
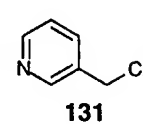
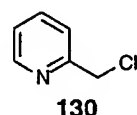
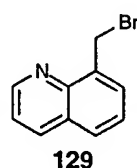
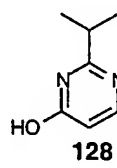
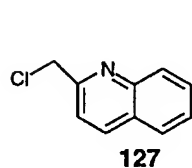
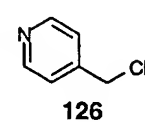
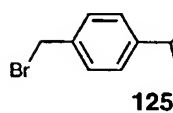
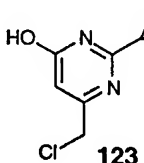
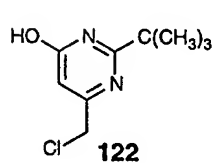
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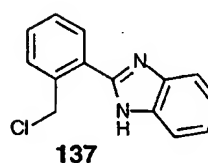
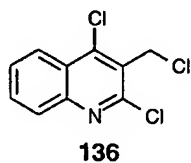
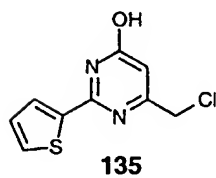
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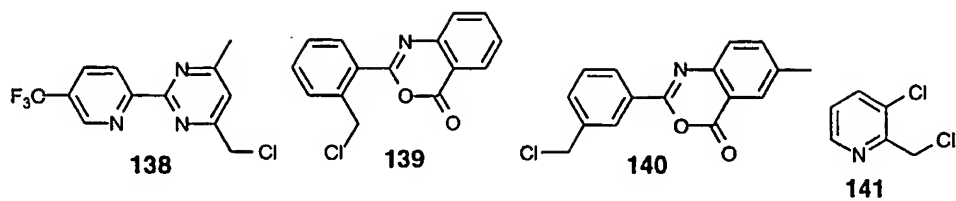


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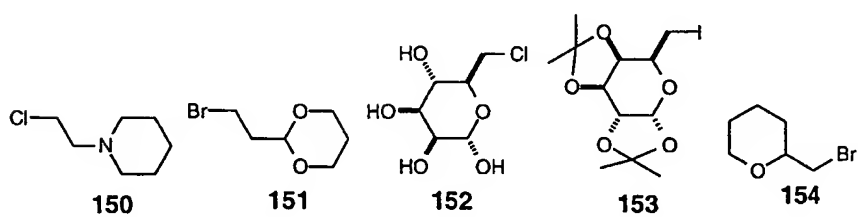
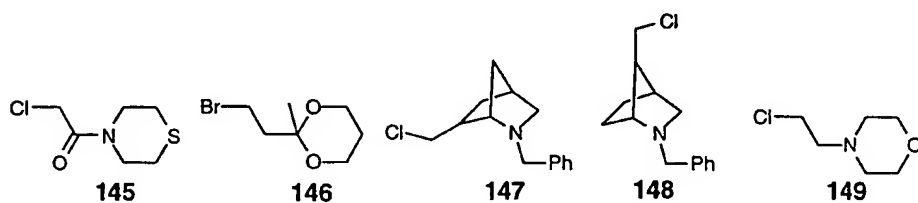
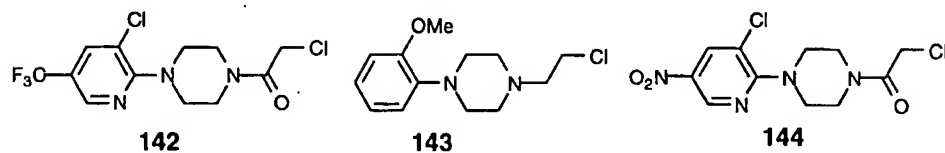


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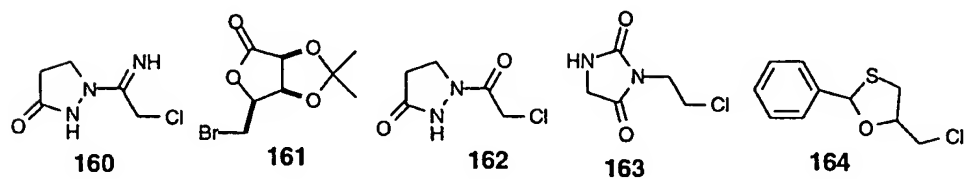
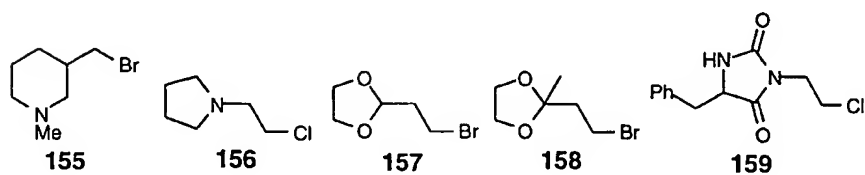




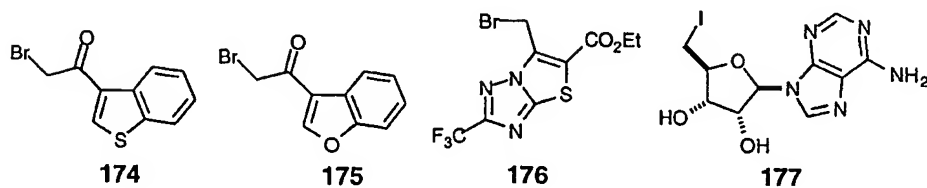
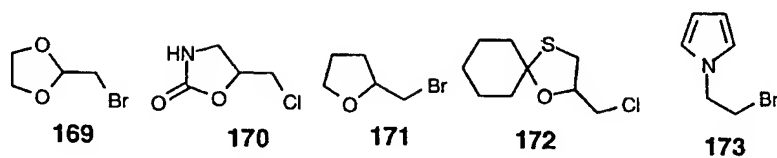
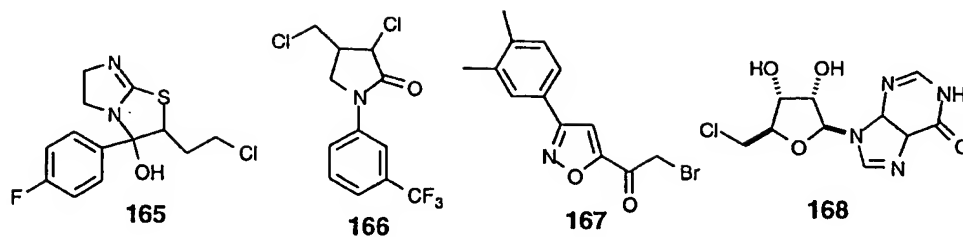
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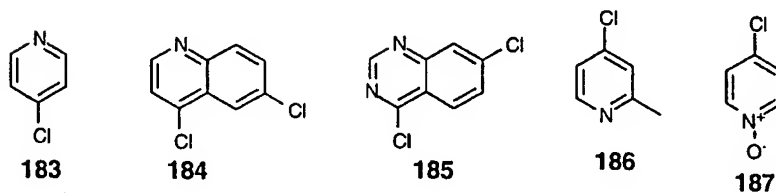
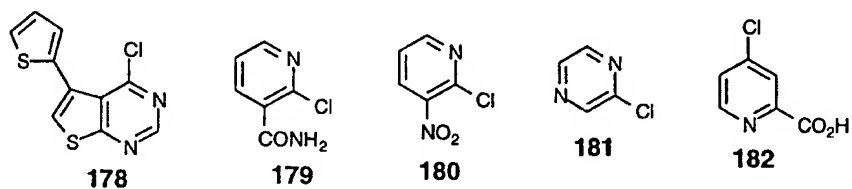
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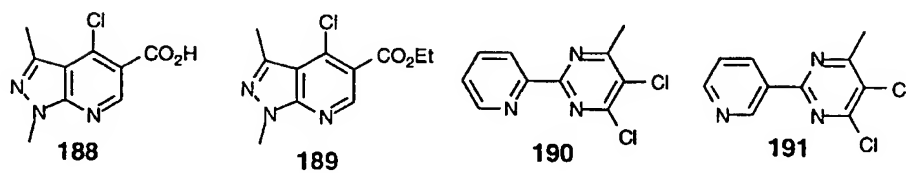
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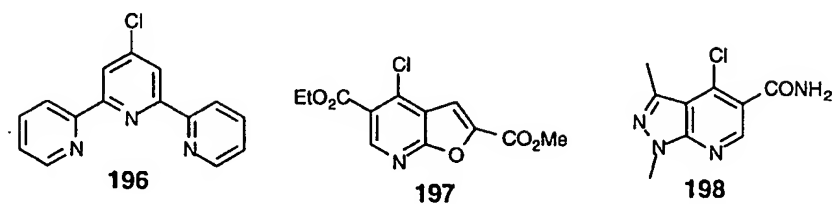
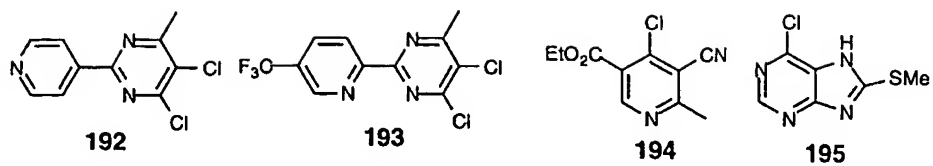


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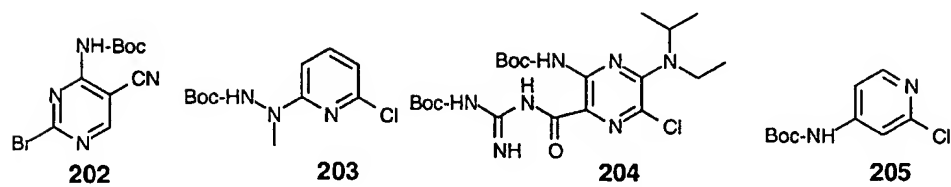
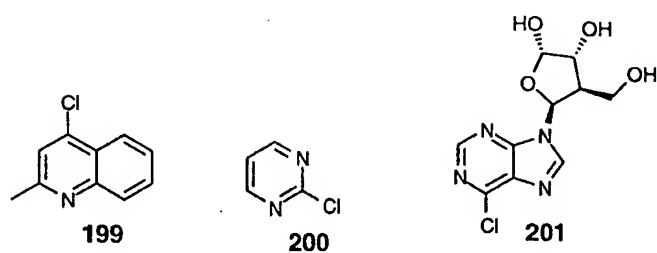


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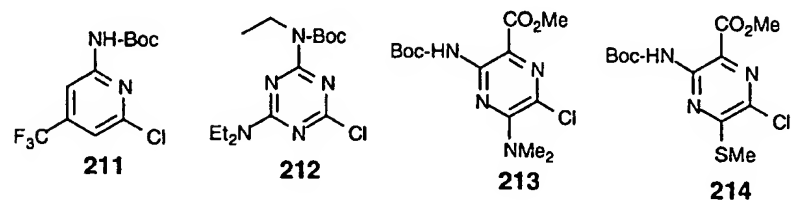
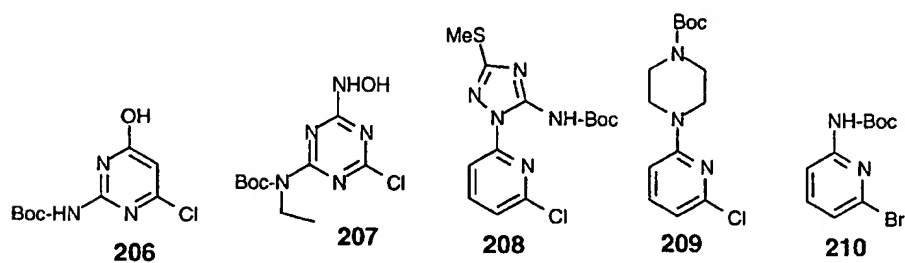




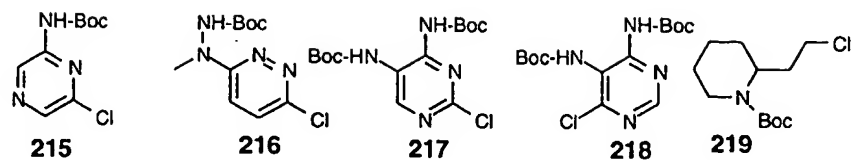
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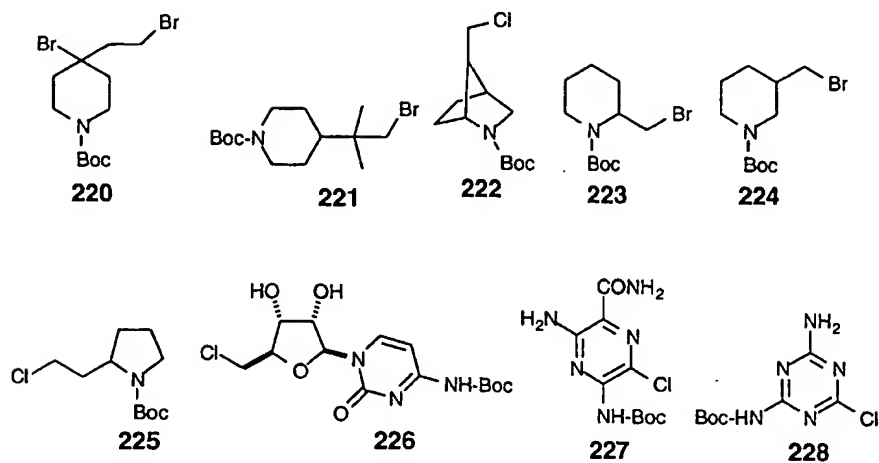
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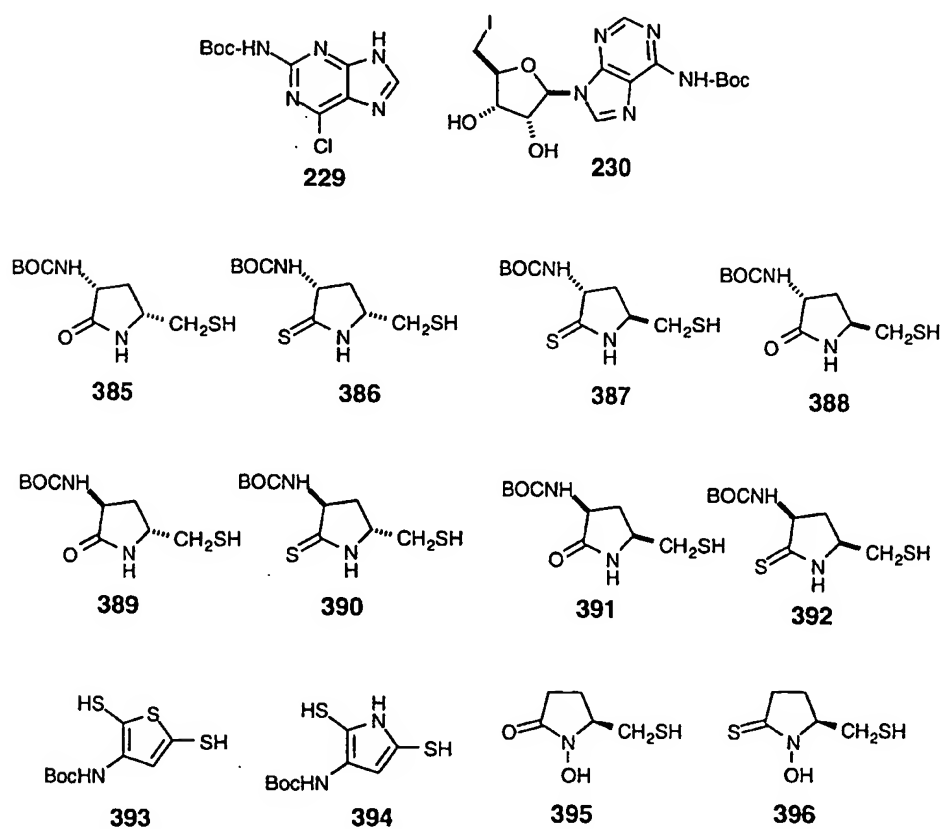
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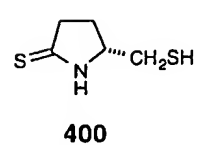
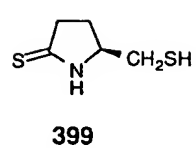
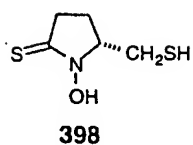
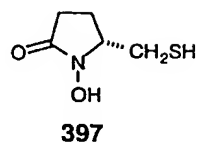


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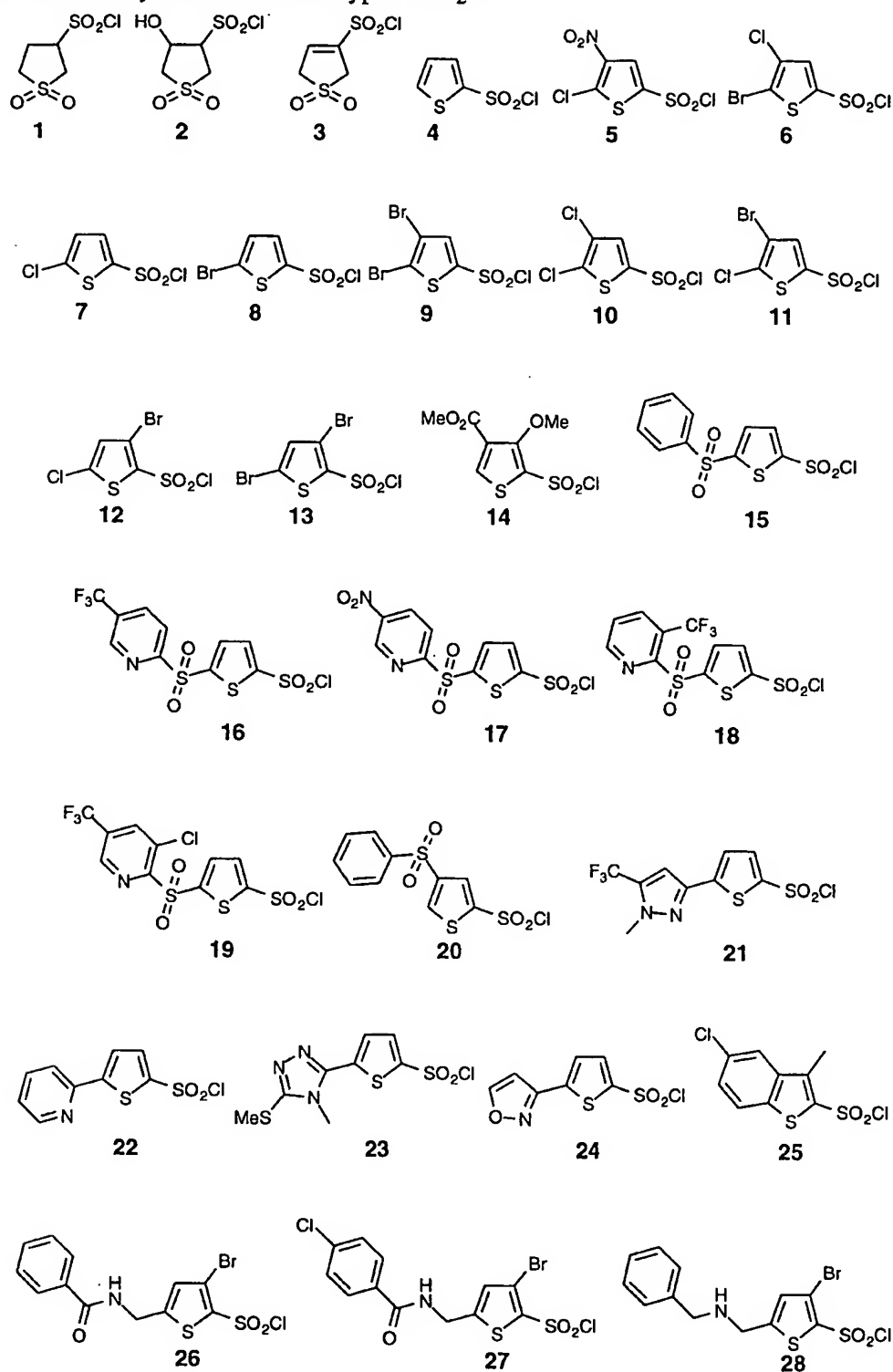


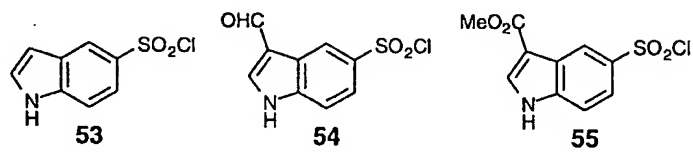
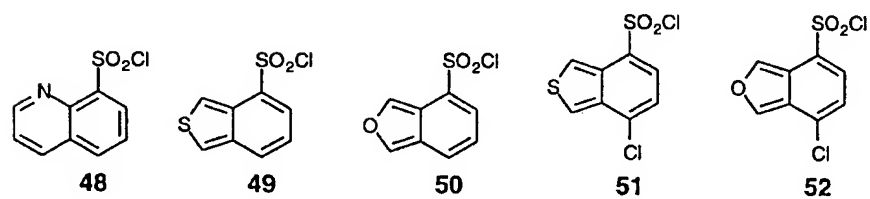
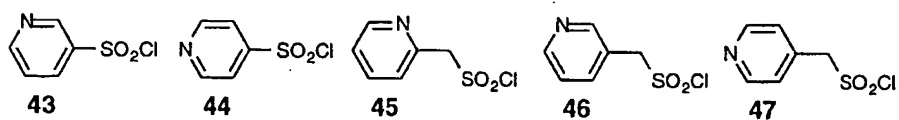
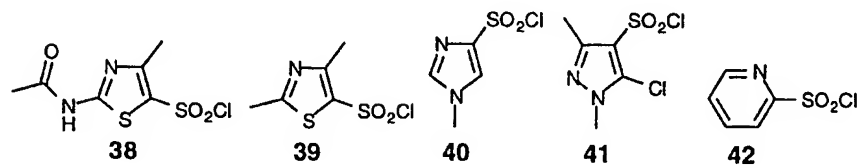
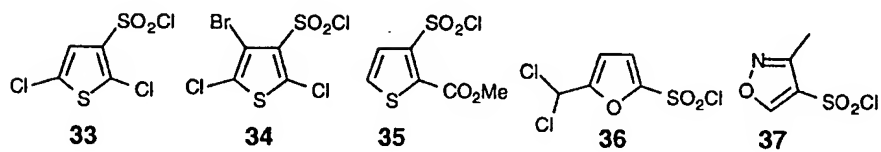
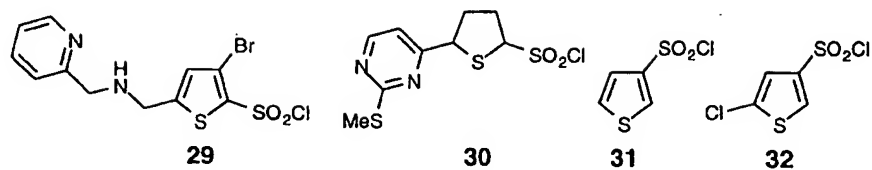
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Table 18. Sulfonyl chlorides of the type A-SO₂Cl



The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept.

3525 In Tables 2-10, the abbreviation bz=benzoyl, bn=benzyl, Ph=phenyl, BOC=t-butyloxycarbonyl and TS=p-toluenesulfonyl.

Compound 1

(3-(Aminomethyl)benzoyl)-Met-OCH₃

3530

Step A

(3-(Chloromethyl)benzoyl)-Met-OCH₃

To a solution of methionine methyl ester hydrochloride (2.0 g, 10 mmol) and 3-(chloromethyl)benzoyl chloride (2.08 g, 11.0 mmol) in methylene chloride (50 mL) was slowly added triethylamine (3.07 mL, 22.0 mmol) at ice bath temperature for 2 hours. The mixture was washed with 0.5 N HCl (50 mL x 2), brine (50 mL x 2) and water (50 mL x 2) then dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to give the desired product (3.03 g) as a white solid: m.p. 82-83°C; ¹H NMR (CDCl₃) δ 7.82 (1H, s), 7.74 (1H, d, J=7.7 Hz), 7.53 (1H, d, J=7.7 Hz), 7.42 (1H, t, J=7.7 Hz), 7.06 (1H, br d, J=7.6 Hz), 4.92 (1H, ddd, J=7.6, 7.1, 5.1 Hz), 4.59 (2H, s), 3.78 (3H, s), 2.58 (2H, t, J=7.1 Hz), 2.26 (1H, sm), 2.15 (1H, m), 2.10 (3H, s); ¹³C NMR (CDCl₃) δ 172.59, 166.54, 138.13, 134.25, 131.95, 129.12, 127.42, 126.97, 52.72, 52.14, 45.55, 31.47, 30.12, 15.55.

3545

Step B

(3-(Azidomethyl)benzoyl)-Met-OCH₃

A suspension of (3-(chloromethyl)benzoyl)-Met-OCH₃ (1.58 g, 5.0 mmol) and sodium azide (1.3 g, 20.0 mmol) in DMSO (40 mL) was stirred at 80°C for 7 hours. The mixture was diluted with methylene chloride (100 mL), washed with brine (70 mL x 2) and water (70 mL x 2), and then dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure to give a yellow residue. Chromatography on silica gel (30% ethyl acetate in hexanes) to provide the desired product (1.45 g) as a colorless solid: m.p. 48-49°C; ¹H NMR (CDCl₃) δ 7.78 (2H, m), 7.49 (2H, m), 6.99 (1H, br d, J=7.4 Hz), 4.49 (1H, ddd, J=7.4, 7.1, 5.2 Hz), 4.42 (2H, s), 3.80 (3H, s), 2.60 (2H, t, J=7.4 Hz), 2.29 (1H, m), 2.17 (1H, m), 2.12 (3H, s); ¹³C NMR (CDCl₃) δ 177.50, 166.54, 135.97, 134.06, 131.18, 128.89, 126.84, 126.71, 54.09, 52.47, 51.95, 31.38, 30.00, 15.30.

Step C

(3-(Aminomethyl)benzoyl)-Met-OCH₃

3560 A suspension of (3-(azidomethyl)benzoyl)-Met-OCH₃ (1.29 g, 4.0 mmol) and 5%
palladium on carbon (0.2 g) in methanol (40 mL) was stirred under a hydrogen atmosphere
(1 atm) for two days at room temperature. The catalyst was removed by filtration through
celite (1.5 g) and the solvent was evaporated in vacuo. The residue was washed with water
(5 mL x 2) and dried to give the desired product (1.12 g) as a colorless foam. ¹H NMR
3565 (CDCl₃) δ 7.81 (1H, s), 7.68 (1H, d, *J*=7.4 Hz), 7.45 (1H, d, *J*=6.5 Hz), 7.36 (1H, t,
J=7.4 Hz), 4.91 (1H, ddd, *J*=7.3, 7.1, 5.1 Hz), 3.90 (2H, s), 3.77 (3H, s), 3.21 (2H, br
s), 2.59 (2H, t, *J*=7.4 Hz), 2.20 (1H, m), 2.12 (1H, m), 2.09 (3H, s).

Compound 2

3570 (4-(Aminomethyl)benzoyl)-Met-OCH₃

The title compound is prepared according to the procedure used to prepare Compound 1 but
replacing 3-(chloromethyl)benzoyl chloride with 4-(chloromethyl)benzoyl chloride.

Compound 3

3575 (3-Aminobenzoyl)-Met-OCH₃

The title compound was prepared according to the procedure described in J. Biol. Chem.
269 12410-12413 (1994).

Compound 4

3580 (4-Aminobenzoyl)-Met-OCH₃

Step A

N-BOC-4-Aminobenzoic acid

4-Aminobenzoic acid (10 g, 72.9 mmol) was placed into a mixture of dioxane (145.8 mL)
3585 and 0.5 M NaOH (145.8 mL). The solution was cooled to 0°C and di-*t*-butyl dicarbonate
(23.87 g, 109.5 mmol) was added. The reaction mixture was allowed to warm to room
temperature and stirred overnight. The next day, the dioxane was removed, the residue was
made acidic and extracted into ethyl acetate. The ethyl acetate fractions were combined and
washed with 1N HCl to remove any unreacted starting material. The solution was dried
3590 over Na₂SO₄ and the solvent was removed in vacuo. The crude material was recrystallized
from ethyl acetate/hexanes to provide the desired product (12.2 g): m.p. 189-190°C; ¹H
NMR (CD₃OD) δ 1.52 (9H, s), 7.49 (2H, d, *J*=8.6 Hz), 7.91 (2H, d, *J*=8.6 Hz), 9.28
(1H, s); ¹³C NMR (CD₃OD) δ 28.59, 81.29, 118.54, 125.30, 131.81, 145.70, 155.00,

169.80; Anal. Calc. for $C_{12}H_{15}NO_4$, C: 60.76, H: 6.37, N: 5.90; Found, C: 60.52, H: 6.43, N: 5.83; HRMS Calc. for $C_{12}H_{15}NO_4$, 237.0961, Found, 237.1001.

Step B

(N-BOC-4-Aminobenzoyl)-Met-OCH₃

Into a dried, nitrogen filled flask was placed N-BOC-4-aminobenzoic acid (8.77 g, 36.97 mmol) in dry methylene chloride (148 mL) along with methionine methyl ester hydrochloride (8.12 g, 40.66 mmol). This solution was cooled in an ice bath and triethylamine (6.7 mL), EDCI (7.80 g, 40.66 mmol) and hydroxybenzotriazole (HOBT, 5.50 g, 40.66 mmol) were added. The mixture was stirred overnight, diluted with more methylene chloride and was extracted three times each with 1 M HCl, 1M NaHCO₃ and water. The methylene chloride was dried over MgSO₄ and the solvent was removed in vacuo. The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (9.72 g): m.p. 184-185°C; ¹H NMR (CDCl₃) δ 1.53 (9H, s), 2.06-2.18 (4H, m), 2.23-2.33 (1H, m), 2.59 (2H, t, J=7.6 Hz), 3.80 (3H, s), 4.92 (1H, m), 7.45 (2H, d, J=8.7 Hz), 7.77 (2H, d, J=8.7 Hz); ¹³C NMR (CDCl₃) δ 15.59, 28.34, 30.15, 31.64, 52.10, 52.73, 81.20, 117.73, 127.8, 128.33, 141.88, 152.33, 166.50, 172.75; Anal. Calc. for $C_{18}H_{26}N_2O_5S$, C: 56.53, H: 6.85, N: 7.29; Found, C: 56.47, H: 6.86, N: 7.29; m/z (EI) 382 (M).

Step C

(4-Aminobenzoyl)-Met-OCH₃ hydrochloride

N-BOC-4-aminobenzoyl-Met-OCH₃ (3.53 g, 9.59 mmol) was placed into methylene chloride (30-35 mL) and to it was added 3M HCl/EtO₂ (38.4 mL). After standing, a white precipitate formed. After two hours the solution was decanted and the crystals were collected by centrifugation. The crystals were then washed several times with fresh ether and dried overnight on the vacuum pump. Meanwhile, the filtrate was left to stand overnight to allow additional product to precipitate. The second fraction was washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 2.87 g: m.p. 158-164°C; ¹H NMR (CDCl₃) δ 2.10 (3H, s), 2.12-2.29 (1H, m), 2.52-2.71 (1H, m), 2.59 (2H, t, J=7.6 Hz), 3.75 (3H, s), 4.79 (1H, m), 7.02 (2H, d, J=8.6 Hz), 7.55 (2H, d, J=8.6 Hz); ¹³C NMR (CDCl₃) δ 15.23, 31.43, 31.53, 52.91, 52.43, 124.35, 130.56, 135.31, 135.76, 168.95, 173.87; HRMS Calc. for $C_{13}H_{18}N_2O_3S$, 282.1038, Found 282.1009.

Compound 5

(4-Amino-3-methylbenzoyl)-Met-OCH₃

Step AN-BOC-4-Amino-3-methylbenzoic acid

4-Amino-3-methylbenzoic acid (5 g, 33.1 mmol) was reacted according to the same
3635 procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The
resulting orange-brown solid was recrystallized from ethyl acetate and hexanes to provide
the desired product (4.99 g) as tan prismatic crystals: m.p. 180-182°C; ¹H NMR (CD₃OD)
d 1.51 (9h, s), 2.27 (3H, s), 7.66 (1H, d, *J*=8.1 Hz), 7.79-7.82 (2H, m), 8.32 (1H, s);
¹³C NMR (CD₃OD) d 17.98, 28.62, 81.47, 123.12, 127.05, 129.14, 130.65, 132.99,
3640 142.45, 155.33, 168.70; Anal. Calc. for C₁₃H₁₇NO₄, C: 62.15, H: 6.82, N: 5.58; Found
C: 62.07, H: 6.86, N: 5.46; m/z (EI) 251; HRMS Calc. for C₁₃H₁₇NO₄, 251.1158;
Found, 251.1153.

Step B(N-BOC-4-Amino-3-methylbenzoyl)-Met-OCH₃

3645 N-BOC-4-amino-3-methylbenzoic acid (2.00 g, 7.96 mmol) was reacted with with
methionine methyl ester hydrochloride (1.75 g, 8.76 mmol), triethylamine (1.4 mL), EDCI
(1.68 g, 8.76 mmol) and hydroxybenzotriazole (HOBT, 1.18 g, 8.76 mmol) in dry
methylene chloride (31.8 mL) according to the procedure described for the preparation of N-
3650 BOC-4-aminobenzoyl)-Met-OCH₃. The resulting solid was recrystallized from ethyl
acetate/hexanes to yield the desired product (2.61 g): m.p. 163-165°C; ¹H NMR (CDCl₃) d
1.54 (9H, s), 2.06-2.18 (4H, m), 2.23-2.34 (4H, m), 2.59 (2H, t, *J*=6.8 Hz), 3.80 (3H,
s), 4.92 (1H, m), 6.45 (1H, s), 6.88 (1H, d, *J*=7.5 Hz), 7.63 (1H, d, *J*=8.6 Hz), 7.66
(1H, s), 8.05 (1H, d, *J*=8.6 Hz); ¹³C NMR (CDCl₃) d 15.47, 17.61, 28.22, 30.03,
3655 31.55, 51.93, 52.57, 81.04, 118.73, 125.62, 127.66, 129.54, 139.89, 152.34, 166.58,
172.66.

Step C(4-Amino-3-methylbenzoyl)-Met-OCH₃ hydrochloride

3660 N-BOC-4-Amino-3-methylbenzoyl)-Met-OCH₃ (0.99 g, 2.59 mmol) was dissolved in
methylene chloride (15-20 mL) and precipitated with 3M HCl/Et₂O (20.7 mL). A pale
orange precipitate was obtained, washed with ether and dried overnight on the vacuum
pump. The total yield of the desired product was 0.83 g: m.p. 157-159°C; ¹H NMR
(CD₃OD) d 2.04 (3H, s), 2.11-2.25 (1H, m), 2.47 (3H, s), 2.52-2.68 (3H, m), 3.74 (3H,
3665 s), 4.75-4.80 (1H, m), 7.48 (1H, d, *J*=8.2 Hz), 7.81 (2H, d, *J*=8.2 Hz), 7.87 (1H, s);
¹³C NMR (CD₃OD) d 15.23, 17.28, 31.43, 31.51, 52.91, 53.37, 124.41, 127.85,

131.99, 133.63, 134.14, 135.65, 169.05, 173.84; Anal. Calc. for $C_{14}H_{21}N_2O_3S$, C: 50.52, H: 6.36, N: 8.42; Found C: 50.71, H: 6.40, N: 8.34.

3670

Compound 6(4-Amino-3-methoxybenzoyl)-Met-OCH₃Step AN-BOC-4-Amino-3-methoxybenzoic acid

3675 4-Amino-3-methoxybenzoic acid (1 g, 5.98 mmol) was reacted according to the same procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The resulting solid was recrystallized from ethyl acetate and hexanes to provide the desired product (1.5 g) as tan crystals: m.p. 176-178°C; ¹H NMR (CD₃OD) δ 1.52 (9H, s), 3.92 (3H, s), 7.56 (1H, s), 7.62 (1H, d, *J*=8.4 Hz), 7.96 (1H, s), 8.03 (1H, d, *J*=8.4 Hz); ¹³C NMR (CD₃OD) δ 28.53, 56.35, 81.78, 112.01, 118.58, 124.20, 125.76, 133.84, 149.04, 154.20, 169.60; HRMS Calc. for $C_{13}H_{17}NO_5$, 267.1107; Found, 267.1103.

3680

Step B(N-BOC-4-Amino-3-methoxybenzoyl)-Met-OCH₃

3685 N-BOC-4-amino-3-methoxybenzoic acid (0.35 g, 1.31 mmol) was reacted with with methionine methyl ester hydrochloride (0.9 g, 1.43 mmol) using EDCI according to the procedure described for the preparation of (N-BOC-4-aminobenzoyl)-Met-OCH₃. The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (0.36 g): m.p. 163-165°C; ¹H NMR (CDCl₃) δ 1.53 (9H, s), 2.09-2.18 (4H, m), 2.23-2.35 (1H, m), 2.60 (2H, t, *J*=6.9 Hz), 3.80 (3H, s), 3.93 (3H, s), 4.92 (1H, br s), 6.93 (1H, d, *J*=7.6 Hz), 7.25 (1H, m), 7.31 (1H, d, *J*=10.2 Hz), 7.44 (1H, s), 8.15 (1H, d, *J*=8.5 Hz); ¹³C NMR (CDCl₃) δ 15.47, 28.23, 30.09, 31.48, 52.06, 52.54, 55.81, 80.82, 98.06, 109.38, 116.66, 119.31, 131.52, 147.23, 152.31, 166.57, 172.58; *m/z* (FAB) 413 (*M* + 1).

3690

3695

Step C(4-Amino-3-methoxybenzoyl)-Met-OCH₃ hydrochloride

N-BOC-4-Amino-3-methoxybenzoyl-Met-OCH₃ (0.71 g, 1.79 mmol) was dissolved in methylene chloride (4 mL) and precipitated with 3M HCl/Et₂O (12 mL). A reddish precipitate was obtained, washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 0.55 g: m.p. 176-177°C; ¹H NMR (CD₃OD) δ 2.08 (3H, s), 2.21 (2H, m), 2.61 (2H, m), 3.74 (3H, s), 4.02 (3H, s), 4.79 (1H, m), 7.50

3700

(1H, d, $J=8.2$ Hz), 7.57 (1H, d, $J=4.1$ Hz), 7.67 (1H, s); ^{13}C NMR (CD_3OD) δ 15.26, 31.34, 31.42, 52.95, 53.38, 57.12, 112.29, 121.43, 124.57, 124.77, 136.15, 153.67, 168.79, 173.81.

Compound 7

(4-Amino-1-naphthoyl)-Met-OCH₃

3710

Step A

4-Amino-1-naphthoic acid

4-Amino-1-naphthalenecarbonitrile (1.5 g, 8.91 mmol) was suspended in a 50% KOH solution (18 mL). The heterogeneous solution was heated at reflux for 2-3 days. Once the solution became homogeneous and TLC showed no more starting material, the deep red solution was cooled and poured over 200 mL of water. The resulting solution was then filtered and the desired product was precipitated with concentrated HCl. The resulting red crystals were filtered and the filtrate was refiltered to give pink crystals. The first fraction of crystals was treated with activated carbon to remove some of the red color. A total of 1.51 g of the desired product was obtained: m.p. 169-171°C; ^1H NMR (CD_3OD) δ 6.69 (1H, d, $J=8.2$ Hz), 7.38-7.43 (1H, m), 7.48-7.54 (1H, m), 8.03 (1H, d, $J=8.5$ Hz), 8.13 (1H, d, $J=8.2$ Hz), 9.09 (1H, d, $J=8.5$ Hz); ^{13}C NMR (CD_3OD) δ 107.39, 114.61, 122.99, 123.92, 125.21, 127.40, 128.48, 135.04, 151.35, 171.44; HRMS Calc. for $\text{C}_{11}\text{H}_7\text{NO}_2$, 187.0633; Found, 187.0642.

3725

Step B

N-BOC-4-Amino-1-naphthoic acid

4-Amino-1-naphthoic acid (0.86 g, 4.61 mmol) was dissolved in dioxane (9.2 mL). Di-*t*-butyl dicarbonate (1.11 g, 5.07 mmol) was added and the mixture was stirred overnight. The reaction mixture was worked up as described above for N-BOC-4-aminobenzoic acid to give 0.76 g of the desired product as a reddish pink solid: m.p. 194-195°C; ^1H NMR (CD_3OD) δ 1.56 (9H, s), 7.53-7.62 (2H, m), 7.79 (1H, d, $J=8.1$ Hz), 8.12 (1H, d, $J=8.0$ Hz), 8.22 (1H, d, $J=8.18$ Hz), 9.02 (1H, d, $J=8.9$ Hz); ^{13}C NMR (CD_3OD) δ 26.68, 81.62, 119.06, 123.40, 124.57, 127.03, 127.37, 128.49, 128.77, 131.89, 133.76, 139.86, 155.95, 170.73; Anal. Calc. for $\text{C}_{17}\text{H}_{17}\text{NO}_4$, C: 66.90, H: 5.96, N: 4.88; Found C: 66.49, H: 6.08, N: 4.79; m/z (EI), 289; HRMS Calc. for $\text{C}_{16}\text{H}_{17}\text{NO}_4$, 287.1158; Found, 287.1151.

Step C

(N-BOC-4-Amino-1-naphthoyl)-Met-OCH₃

3740 N-BOC-4-Amino-naphthoic acid (0.46 g, 1.60 mmol), methionine methyl ester hydrochloride (0.35 g, 1.76 mmol), EDCI (0.43 g, 1.76 mmol), HOBT (0.24 g, 1.76 mmol) and triethylamine (0.27 mL) in methylene chloride (6.4 mL) were reacted as described above for N-BOC-4-aminobenzoyl-Met-OCH₃. After workup and recrystallization from ethyl acetate hexanes, the desired product (0.44 g) was obtained as pale pink crystals: m.p. 131-132°C; ¹H NMR (CDCl₃) δ 1.57 (9H, s), 2.11-2.21 (4H, m), 2.29-2.41 (1H, m), 2.65 (2H, t, *J*=7.1 Hz), 3.83 (3H, s), 4.99-5.06 (1H, m), 6.68 (1H, d, *J*=8.0 Hz), 7.02 (1H, s), 7.56-7.59 (2H, m), 7.69 (1H, d, *J*=7.9 Hz), 7.87-7.90 (1H, m), 8.02 (1H, d, *J*=7.9 Hz), 8.44-8.48 (1H, m); ¹³C NMR (CDCl₃) δ 15.56, 28.31, 30.19, 31.65, 52.06, 52.64, 81.17, 115.82, 120.18, 125.79, 126.37, 126.53, 127.18, 131.02, 135.65, 152.93, 169.04, 172.40; HRMS Calc. for C₂₂H₂₈N₂O₅S, 432.1719; Found, 432.1702; *m/z* (FAB) 433 (*M*+1).

Step D(4-Amino-1-naphthoyl)-Met-OCH₃ hydrochloride

3755 (N-BOC-4-Amino-1-naphthoyl)-Met-OCH₃ (0.57 g, 1.31 mmol) was deprotected with HCl/ether to yield the desired product (0.31 g) as a white solid: m.p. 178-181°C; ¹H NMR (CD₃OD) δ 2.08-2.16 (4H, m), 2.20-2.30 (1H, m), 2.57-2.75 (2H, m), 3.82 (3H, s), 4.87-4.91 (1H, m), 7.59 (1H, d, *J*=7.5 Hz), 7.67 (1H, d, *J*=7.5 Hz), 7.71-7.80 (2H, m), 8.03 (1H, dd, *J*=7.1, 2.0 Hz), 8.35 (1H, dd, *J*=6.8, 1.8 Hz); ¹³C NMR (CD₃OD) δ 15.23, 31.40, 53.01, 53.33, 119.90, 122.20, 126.15, 127.41, 127.77, 129.09, 129.31, 131.50, 132.33, 135.64, 171.77, 173.83; *m/z* (FAB), 369 (*M*+1).

Compound 8(4-Amino-2-phenylbenzoyl)-Met-OCH₃

3765

Step A4-Nitro-2-phenyltoluene

2-Bromo-4-nitrotoluene (2.16 g, 10.00 mmol) and phenylboric acid (1.46 g, 12.00 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added Pd(Ph₃P)₄ (0.58 g, 5%). The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et₂O. The crude product was chromatographed on silica gel using hexanes as eluent. After recrystallization from ethanol, the desired product (1.23 g) was obtained as pale orange needles: m.p. 69-71°C; ¹H NMR (CDCl₃) δ 2.36 (3H, s), 7.29-7.40 (2H, m), 7.41-7.49 (5H, m), 8.07-8.10 (2H, m); ¹³C NMR (CDCl₃)

3775 d 20.68, 121.96, 124.51, 127.78, 128.41, 128.83, 131.06, 139.06, 139.44, 142.97, 143.48, 146.05; Anal. Calc. for $C_{13}H_{11}NO_2$, C: 73.26, H: 5.20, N: 6.57; Found, C: 73.10, H: 5.12, N: 6.50; m/z (EI) 213; HRMS Calc. for $C_{13}H_{11}NO_2$, 213.0790; Found, 213.0793.

3780

Step B

4-Nitro-2-phenylbenzoic acid

4-Nitro-2-phenyltoluene (0.5 g, 2.34 mmol) was dissolved in water (4.6 mL) and pyridine (2.3 mL). The mixture was heated to reflux and $KMnO_4$ (1.85 g, 11.7 mmol) was added. The reaction mixture was heated overnight and the solution was filtered and washed several
3785 times with boiling water. The aqueous solution was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solution was dried over Na_2SO_4 and the solvent removed in vacuo to provide the desired product (0.37 g): m.p. 174-176°C, 1H NMR (CD_3OD) d 7.38-7.48 (5H, m), 7.96 (1H, d, $J=8.5$ Hz), 8.21 (1H, d, $J=2.3$ Hz), 8.28 (1H, dd, $J=8.48, 2.37$ Hz); ^{13}C NMR (CD_3OD) d 122.95, 126.09, 129.27, 129.42,
3790 129.49, 131.56, 139.26, 140.42, 144.41, 150.17, 170.52; m/z (EI) 243 (M).

Step C

(4-Nitro-2-phenylbenzoyl)-Met-OCH₃

4-Nitro-2-phenylbenzoic acid (0.3 g, 1.23 mmol), methionine methyl ester hydrochloride
3795 salt (0.27 g, 1.35 mmol), EDCI (0.26 g, 1.35 mmol), HOBT (0.18 g, 1.35 mmol) and triethylamine (0.19 mL) in dry methylene chloride (4.9 mL) were reacted according the procedure described above for (N-BOC-4-aminobenzoyl)-Met-OCH₃. After recrystallization of the product from ethyl acetate hexanes, the desired product (0.41 g) was obtained: m.p. 98-101°C; 1H NMR ($CDCl_3$) d 1.62-1.73 (1H, m), 1.79-1.88 (1H, m),
3800 1.91 (3H, s), 1.99 (2H, t, $J=7.2$ Hz), 3.59 (3H, s), 4.53 (1H, m), 6.45 (1H, d, $J=7.8$ Hz), 7.33-7.40 (5H, m), 7.67 (1H, d, $J=8.3$ Hz), 8.07-8.12 (2H, m); ^{13}C NMR ($CDCl_3$) d 14.92, 29.11, 30.67, 51.51, 52.29, 121.86, 124.74, 128.27, 128.60, 128.69, 129.52, 137.50, 140.56, 141.02, 148.09, 167.23, 171.23; m/z (FAB), 389 (M+1).

3805

Step D

(4-Amino-2-phenylbenzoyl)-Met-OCH₃

(4-Nitro-2-phenylbenzoyl)-Met-OCH₃ (0.35 g, 0.90 mmol) was dissolved in ethyl acetate (9.0 mL). To this mixture was added $SnCl_2 \cdot 2H_2O$ (1.02 g, 4.5 mmol) and the reaction
3810 mixture was heated under nitrogen at reflux for one hour. The mixture was poured onto ice, the solution was made basic using $NaHCO_3$ and the product was extracted into ethyl acetate several times (7-8). The ethyl acetate solutions were combined, washed with brine and

dried over Na_2SO_4 . The solvent was removed in vacuo to the desired product (0.24 g) as a yellow solid: ^1H NMR (CDCl_3) δ 1.58-1.70 (1H, m), 1.80-1.92 (1H, m), 1.98 (3H, s), 2.06 (2H, t, $J=7.7$ Hz), 3.62 (3H, s), 4.00 (2H, br s), 4.56-4.63 (1H, m), 5.84 (1H, d, $J=7.7$ Hz), 6.50 (1H, s), 6.61 (1H, d, $J=8.4$ Hz) 7.29-7.42 (5H, m), 7.58 (1H, d, $J=8.3$ Hz); ^{13}C NMR (CDCl_3) δ 15.02, 29.25, 31.25, 51.57, 52.15, 113.27, 115.88, 123.52, 127.56, 128.37, 128.44, 130.92, 140.66, 141.44, 148.53, 168.58, 171.91.

Compound 9

3820 (4-Amino-2-(2-thienyl)benzoyl)-Met-OCH₃

The title compound can be prepared according to the method used to prepare Compound 8, only substituting thiophene-2-boronic acid for phenyl boronic acid.

Compound 10

3825 (4-Amino-2-(1-naphthyl)benzoyl)-Met-OCH₃

The title compound can be prepared according to the method used to prepare Compound 8, only substituting 1-naphthylboronic acid for phenylboronic acid.

Compound 11

3830 4-Amino-3'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Compound 12

3835 4-Amino-4'-biphenyl carboxylic acid

Step A

4-Nitro-4'-methylbiphenyl

3840 The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-4-methylbenzene.

Step B

4-Nitro-4'-biphenyl carboxylic acid

3845 The title compound was prepared by KMnO_4 oxidation of 4-nitro-4'-methylbiphenyl.

Step C

4-Amino-4'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-4'-biphenyl carboxylic acid.

3850

Compound 13

4-Amino-3'-biphenyl carboxylic acid

Step A

3855

4-Nitro-3'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Step B

3860

4-Nitro-3'-biphenyl carboxylic acid

The title compound was prepared by KMnO_4 oxidation of 4-nitro-3'-methylbiphenyl.

Step C

4-Amino-3'-biphenyl carboxylic acid

3865

The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-3'-biphenyl carboxylic acid.

Compound 14

4-Amino-2-methoxy-3'-biphenyl carboxylic acid

3870

Step A

2-Methoxy-4-nitro-3'-methylbiphenyl

The title compound was prepared by reaction of 1-bromo-2-methoxy-4-nitrobenzene with 3-methylphenylboronic acid in the presence of palladium acetate.

3875

Step B

2-Methoxy-4-nitro-3'-biphenylcarboxylic acid

The title compound was prepared by KMnO_4 oxidation of 2-methoxy-4-nitro-3'-methylbiphenyl.

3880

Step C

4-Amino-2-methoxy-3'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 2-methoxy-4-nitro-3'-biphenyl carboxylic acid.

3885

Compound 154-Amino-2-isopropoxy-3'-biphenyl carboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

3890

Compound 164-Amino-2-phenyl-3'-biphenylcarboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

3895

Compound 17(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃Step A

3900

2-Bromo-4-nitrobenzoic acid

3905

3910

2-Bromo-4-nitrotoluene (5.0 g, 23.14 mmol) was dissolved in pyridine (23 mL) and water (46 mL). The heterogeneous mixture was heated to 60°C and KMnO₄ (18.29 g, 115.7 mmol) was added carefully. The mixture was then heated under reflux overnight. The reaction mixture was filtered and washed with boiling water. The solution was then made acidic and extracted into ethyl acetate, dried over Na₂SO₄ and the solvent was removed in vacuo. The crude product was dissolved in aqueous NaOH and washed with hexanes. The aqueous phase was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solutions were combined and dried over Na₂SO₄ and the solvent was removed in vacuo to provide the desired product (3.72 g): m.p. 158-160°C; ¹H NMR (CD₃OD) δ 7.81 (1H, d, J=8.5 Hz), 8.08 (1H, d, J=8.5 Hz), 8.30 (1H, s); ¹³C NMR (CD₃OD) δ 121.96, 122.75, 129.36, 132.24, 139.52, 149.54, 167.75; Anal. Calc. for C₇H₄BrNO₄ • 0.1 ethyl acetate, C: 34.88, H: 1.90, N: 5.50; Found, C: 34.68, H: 1.86, N: 5.82.

Step B

3915

3,5-Dimethylphenylboronic acid

3920

Magnesium turnings (1.44 g, 59.43 mmol) were covered with dry THF (18.8 mL) in a dried, nitrogen filled flask fitted with an addition funnel and reflux condenser. To this was added 5-bromo-m-xylene (10 g, 54.03 mmol) in THF (15 mL) after initiation of the Grignard reaction. The addition was carried out over several minutes and the reaction mixture was heated at reflux for 1-2 hours until most of the magnesium had reacted. The reaction mixture was then cooled and transferred to an addition funnel fitted to a nitrogen

filled flask containing triisopropyl borate (24.9 mL) at -70°C. The dropwise addition was carried out over several minutes and the mixture warmed to room temperature and stirred overnight. The grey solution was poured onto 2 M HCl and immediately turned yellow.
3925 The solution was extracted with Et₂O and the Et₂O fractions were combined, dried over MgSO₄ and the solvent was removed in vacuo to provide the desired product (2.41 g): m.p. 249-251°C; ¹H NMR (CDCl₃) δ 2.44 (6H, s), 7.23 (1H, s), 7.84 (2H, s); ¹³C NMR (CD₃OD) δ 21.36, 133.28, 134.39, 137.48.

3930

Step C4-Nitro-2-(3,5-dimethylphenyl)benzoic acid

2-Bromo-4-nitrobenzoic acid (0.43 g, 2.03 mmol) and 3,5-dimethylphenyl boronic acid (0.334 g, 2.23 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added Cs₂CO₃ (1.66 g, 5.08 mmol) followed by Pd(Ph₃P)₄ (0.12 g, 5%).
3935 The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et₂O. It was dried over MgSO₄ and the solvent was removed in vacuo. The crude product was chromatographed on silica gel using a 9:1 mixture of hexanes and ethyl acetate to provide the desired product (0.34 g): ¹H NMR (CDCl₃) δ 2.36 (6H, s), 6.99 (2H, s), 7.07 (1H, s), 8.03 (1H, d, J=9.0 Hz), 8.23-8.25 (2H, m); ¹³C NMR (CDCl₃) δ
3940 21.28, 121.68, 123.68, 125.74, 126.07, 130.22, 131.19, 131.31, 135.04, 138.21, 144.74, 170.75.

Step D(4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃

3945 4-Nitro-2-(3,5-dimethylphenyl)benzoic acid (0.15 g, 0.55 mmol), methionine methyl ester hydrochloride (0.11 g, 0.55 mmol), EDCI (0.11 g, 0.55 mmol), HOBT (0.07 g, 0.55 mmol) and triethylamine (0.08 mL) in dry methylene chloride (2.2 mL) were reacted and worked up according to the procedure for (N-BOC-4-aminobenzoyl)-Met-OCH₃ as described above. After recrystallization from ethyl acetate and hexanes, the desired product
3950 was obtained (0.13 g): m.p. 122-124°C; ¹H NMR (CDCl₃) δ 1.2-1.84 (1H, m), 1.85-1.97 (1H, m), 2.01 (3H, s), 2.05 (3H, t, J=7.7 Hz), 2.38 (6H, s), 3.70 (3H, s), 4.67-4.74 (1H, m), 6.03 (1H, d, J=7.9 Hz), 7.05 (2H, s), 7.09 (1H, s), 7.84-7.87 (1H, m), 7.84-7.87 (1H, m) 8.23-8.26 (2H, m); ¹³C NMR (CDCl₃) δ 15.20, 21.26, 29.22, 31.15, 51.79, 52.57, 122.07, 125.11, 126.27, 130.03, 130.53, 137.77, 138.82, 140.29, 141.56,
3955 148.41, 167.14, 171.53.

Step E(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃

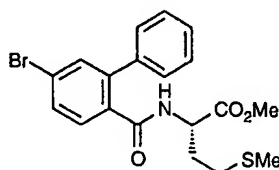
3960 (4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃ (0.11 g, 0.26 mmol) was dissolved in ethyl acetate (3.0 mL). To this mixture was added SnCl₂ · 2H₂O (0.3 g, 1.30 mmol) and the reaction was heated under nitrogen at reflux for 6 hours. The mixture was worked up as described above for (4-amino-2-phenylbenzoyl)-Met-OCH₃ to give the desired product (0.15 g): ¹H NMR (CDCl₃) δ 1.60-1.70 (1H, m), 1.80-1.90 (1H, m), 1.99 (3H, s), 2.05 (2H, t, *J*=7.6 Hz), 2.33 (6H, s), 3.64 (3H, s), 3.93 (2H, br s), 4.61-4.64 (1H, m), 5.82 (1H, d, *J*=7.7 Hz), 6.49 (1H, d, *J*=2.3 Hz), 6.62 (1H, dd, *J*=8.4, 2.4 Hz), 6.98 (2H, s), 7.00 (1H, s), 7.65 (1H, d, *J*=8.3 Hz); ¹³C NMR (CDCl₃) δ 15.08, 21.17, 29.28, 31.49, 51.70, 52.18, 113.30, 115.94, 123.55, 126.36, 129.32, 131.23, 138.15, 140.72, 141.92, 148.40, 168.45, 172.01.

3970

Preparation 1Anilines of the formula B-NH₂

The anilines from Table 1, entries 10-126 (B-NH₂) are prepared using the procedures for Compounds 1-18 with the exception that methionine methyl ester is replaced by methioninesulfone methyl ester, (S-Me)cysteine methyl ester, serine methyl ester, (O-Me)serine methyl ester, (O-Me)homoserine methyl ester, homoserine lactone, isoleucine methyl ester, leucine methyl ester, norleucine methyl ester, norvaline methyl ester, cyclohexylalanine methyl ester, phenylalanine methyl ester, or glutamic acid dimethyl ester.

3980

Preparation 24-Bromo-2-phenylbenzoyl methionine methyl ester

3985

Preparation 2A4-Bromo-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous HBr is treated with NaNO₂ (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

Preparation 2B4-Bromo-2-phenylbenzoic acid

3995 To a solution of the resultant compound from Preparation 2A (1.0 equivalent) in a 3:1 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Preparation 2C4-Bromo-2-phenylbenzoyl methionine methyl ester

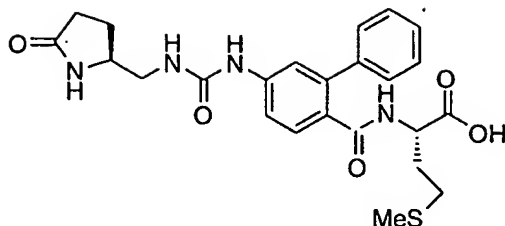
4000 To a solution of the resultant compound from Preparation 2B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged
4005 complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Preparation 2D4-Bromo-2-phenylbenzoyl methionine methyl ester alternate procedure

4010 A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous HBr is treated with NaNO₂ (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC
4015 analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

Preparation 3Arylbromides of the formula B-Br

4020 The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Preparation 2 to provide the arylbromides listed in Table 2.



4025

Example 14-(((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionineExample 1AMethyl 4-(((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoate

4030 To a solution of methyl 4-amino-2-phenylbenzoate hydrochloride (1.0 equivalent) in toluene is added triphosgene (0.33 equivalent) and the mixture is heated at reflux until judged complete by TLC analysis. The intermediate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (2.0 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with

4035 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 1B4-(((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoic acid

4040 To a solution of the resultant compound from Example 1A (1.0 equivalent) in a 3:1 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

4045

Example 1C4-(((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester

4050 To a solution of the resultant compound from Example 1B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

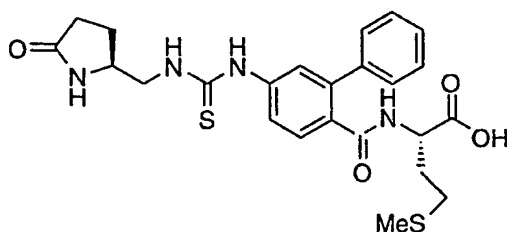
4055

Example 1D4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

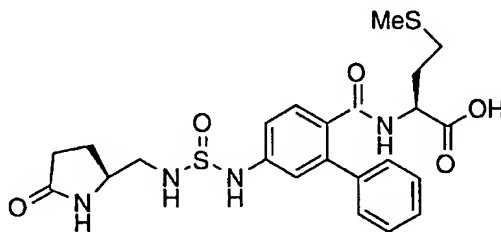
To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and triethylamine (2.0 equivalents). The intermediate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 1E4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 1C in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Example 24-((S)-2-Pyrrolidone-5-aminomethylthiocarbonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

Example 3

4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine

4085

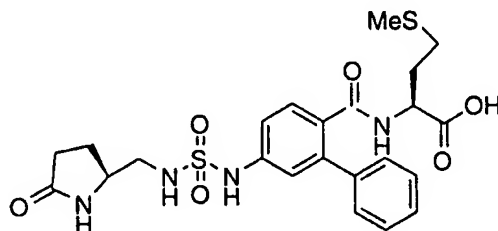
Example 3A4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine methyl ester

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added thionyl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

4095

Example 3B4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 3A in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.



4105

Example 44-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionineExample 4A4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

4110

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added sulfuryl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

4115

Example 4B4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate procedure

4120 A solution of 1 equivalent of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and sulfonyl chloride (1.0 equivalent) in acetonitrile with a catalytic amount of antimony(V) chloride is heated to reflux until judged complete by TLC analysis. The solution is then cooled, filtered, and all volatiles are removed under reduced pressure. The residue is taken up in dichloromethane and treated with triethylamine (1 equivalent and (S)-

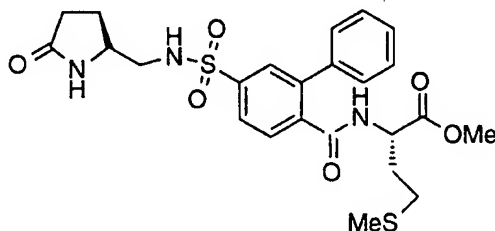
4125 5-aminomethyl-2-pyrrolidone (1.0 equivalent). When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 4C

4130 4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

The resultant compound from Example 4A is hydrolyzed according to the procedure of Example 1B to give the title product.

4135

Example 54-((S)-2-Pyrrolidone-5-methylaminosulfonyl)-2-phenylbenzoyl methionine

4140

Example 5A4-Chlorosulfonyl-2-phenylbenzoic acid methyl ester

To a solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists. The chlorodiazonium salt is poured into a solution of sulfur dioxide (10 equivalents), copper

4145 (II) chloride (0.5 equivalent) and KCl (1.1 equivalents) in dioxane. When TLC analysis indicated that the reaction is complete, the mixture is diluted with water and extracted into benzene which is dried and evaporated to give the title sulfonyl chloride

Example 5B4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoic acid methyl ester

To a solution of the resultant compound from Example 5A (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

Example 5C4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 5B is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 5D4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoyl methionine methyl ester

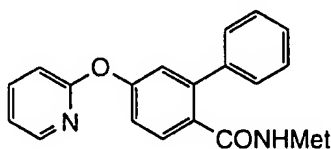
To a solution of the resultant compound from Example 5C (1.0 equivalent) in (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 5E4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists at which time the chlorodiazonium salt will be treated with gaseous sulfur dioxide and copper (II) chloride to give the sulfonyl chloride (0.1 equivalent). This intermediate is reacted with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent) according to the procedure of Example 5B to give the title compound.

Example 5F4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 5D (1.0 equivalent) in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.



Example 6

4-(2-pyridyloxy)-2-phenylbenzoylmethionine

Example 6A

4-Hydroxy-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous H₂SO₄ is treated with NaNO₂ (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by chromatography on silica gel.

Example 6B

4-(2-Pyridyloxy)-2-phenylbenzoic acid methyl ester

A solution of the resultant phenol from Example 6A (1.0 equivalent) is treated with 2-bromopyridine (1.0 equivalent) in the presence of a NaH (1.0 equivalent), or K₂CO₃ (2.0 equivalents) and copper (1.0 equivalent) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 6C

4-(2-Pyridyloxy)-2-phenylbenzoic acid

A solution of the resultant ester from Example 6B (1.0 equivalent) in aqueous methanol is treated with NaOH (2.0 equivalents) and stirred until the reaction is deemed complete by TLC analysis. The mixture is acidified, diluted with water, and extracted into ethyl acetate which is dried and evaporated. Chromatography on silica gel provides the title product.

Example 6D

4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester

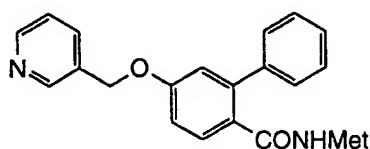
4220 The resultant product from Example 6C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 6E4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester, alternate procedure

4225 A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with NaNO_2 (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated to form the phenol which is purified by chromatography on silica gel. A solution of this phenol (1.0 equivalent) is treated with 3-bromopyridine (1.0 equivalent) in the presence of a NaH (1.0 equivalent), or K_2CO_3 (2.0 equivalents) and copper (1.0 equivalent) in DMF or
4230 pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 6F4-(2-pyridyloxy)-2-phenylbenzoylmethionine

4235 The resultant compound from Example 6E is hydrolyzed according to the procedure of Example 1B to give the title compound.

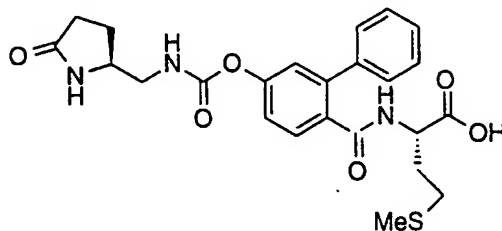


4240

Example 74-(3-pyridylmethylenoxy)-2-phenylbenzoylmethionine

The title compound is prepared as described in Example 6 with the exception that 2-bromopyridine is replaced by 3-chloromethylpyridine hydrochloride.

4245



Example 8

4250 4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

Example 8A

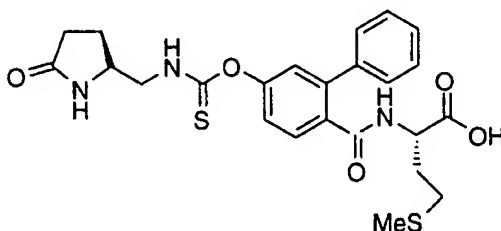
4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine methyl ester

To a solution of 4-hydroxy-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) from
 4255 Example 6E in methylene chloride is added a solution of phosgene in toluene (1.0
 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged
 complete by TLC analysis, the solvent is evaporated with toluene chasers. The
 chloroformate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone
 (1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged
 4260 complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl
 and brine, evaporated, and purified by chromatography on silica gel.

Example 8B

4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

4265 The resultant compound from Example 8A is hydrolyzed according to the procedure of
 Example 1B to give the title product.

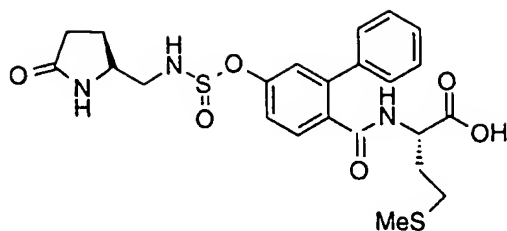


4270

Example 9

4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxy-2-phenylbenzoyl methionine methyl ester

The title compound is prepared as described in Example 8 with the exception that phosgene
 4275 in toluene is replaced by thiophosgene.

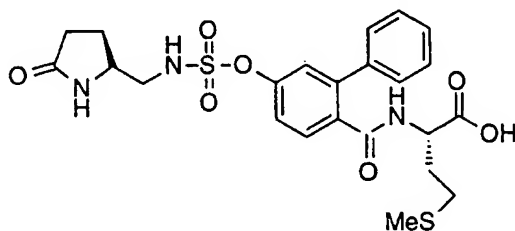


4280

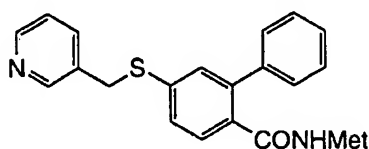
Example 104-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyloxy-2-phenylbenzoic acid methyl ester

The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride.

4285

Example 114-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyloxy-2-phenylbenzoic acid methyl ester

4290 The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by sulfuric chloride.



4295

Example 124-(3-Pyridylmethylthio)-2-phenylbenzoic acid methyl esterExample 12A4-Mercapto-2-phenylbenzoic acid methyl ester

4300

A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with NaNO_2 (1.1 equivalents) to form the diazonium salt. The reaction is

4305 treated with S₈ (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel.

Example 12B

4-(2-Pyridylmethylenethio)-2-phenylbenzoic acid methyl ester

4310 A solution of the resultant thiophenol (1.0 equivalent) from Example 12A is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

4315

Example 12C

4-(2-Pyridylthiomethylen)-2-phenylbenzoic acid

The resultant compound from Example 12B is hydrolyzed according to the procedure of Example 6C to give the title acid.

4320

Example 12D

4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester

4325 The resultant product from Example 12C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 12E

4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 1

4330 A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H₂SO₄ is treated with NaNO₂ (1.1 equivalents) to form the diazonium salt. The reaction is treated with S₈ (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. The thiophenol is purified by chromatography on silica gel. A solution of this
4335 thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

4340

Example 12F

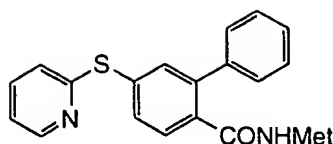
4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 2
Methyl 4-amino-2-phenylbenzoate (100 mmol) is mixed in 50% sulfuric acid, and is cooled by a ice-water bath. To the above mixture with good stirring is added slowly a cold solution of sodium nitrite (110 mmol) in water, the reaction temperature is kept under 10 °C.
4345 Powdered anhydrous sodium carbonate (100 mmol) is carefully added to the cold reaction mixture in small portions, until the reaction mixture reaches pH 7 to 8. Then, the reaction mixture is added in small portions to a solution of sodium p-methoxybenzylsulfide (prepared from reaction 110 mmol of p-methoxybenzylthiol with 55 mmol of 2.0 M NaOH aqueous solution). After completion of the addition, the reaction mixture is refluxed until
4350 judged complete by TLC analysis. The reaction mixture is then extracted with ether, and the organic extracts are washed sequentially with aqueous sodium carbonate solution, water and brine, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The product thus obtained
4355 is dissolved in methanol and water, followed by addition of lithium hydroxide (200 mmol), and the mixture is refluxed until hydrolysis is judged complete by TLC analysis. The reaction mixture is then acidified with 6 N HCl, and extracted into ethyl acetate. The organic extracts are washed with brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. The crude product obtained is redissolved in methylene chloride,
4360 followed by addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.1 equivalent) and 1-hydroxybenzotriazol (1.2 equivalent). The reaction is stirred until it is judged complete by TLC analysis, and then is diluted with ether. The mixture is washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The resulting product
4365 is dissolved in trifluoroacetic acid and anisole (1.5 equivalent), and mercury diacetate (1.2 equivalent) is added. After TLC shows no starting material left, the reaction mixture is diluted with ether, washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting crude material is purified by column chromatography to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. A solution
4370 of this thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

4375

Example 12G4-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

The resultant compound from Example 12D is hydrolyzed according to the procedure of Example 1B to give the title product.

4380

Example 134-(2-Pyridylthio)-2-phenylbenzoylmethionine

4385

Example 13A4-Fluoro-2-phenyl benzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous HBF_4 is treated with NaNO_2 (1.1 equivalents) until an excess of nitrous acid persists. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by chromatography on silica gel.

4390

Example 13B4-Fluoro-2-phenyl benzoic acid

4395

The resultant compound from Example 13A is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 13C4-Fluoro-2-phenyl benzoyl methionine methyl ester

4400

The resultant product from Example 13B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 13D4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester

4405

A mixture of the resultant fluorobenzoate from Example 13C (1.0 equivalent) and 2-mercaptopyridine (1.0 equivalent) is treated with K_2CO_3 (2.0 equivalents) or NaH (1.0 equivalent) in DMF or DMSO and is stirred until the reaction is judged complete by TLC analysis. The mixture is diluted with water and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

4410

Example 13E4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 1

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with NaNO_2 (1.1 equivalents) to form the diazonium salt. The

4415 reaction is treated with S₈ (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel. A solution of this thiophenol (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalent), or K₂CO₃ (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and
4420 chromatography on silica gel.

Example 13F

4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 2

A solution of the resultant thiophenol from Example 12A (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalents),
4425 or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel. The resultant ester is hydrolyzed according to the procedure of Example 6C and then is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

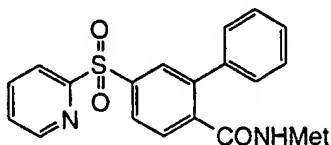
4430

Example 13G

4-(2-Pyridylthio)-2-phenylbenzoylmethionine

The resultant compound from Example 13D is hydrolyzed according to the procedure of Example 1B to give the title product.

4435



Example 14

4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

4440

Example 14A

4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid methyl ester

A solution of 4-(2-pyridylthio)-2-phenylbenzoic acid methyl ester (Example 13F) is
4445 carefully treated with two equivalents of *meta*-chloroperbenzoic acid in methylene chloride at low temperature and the reaction is then quenched with aqueous Na₂SO₃ when judged complete by TLC analysis. The layers are separated and the organic phase is extracted with

aqueous NaHCO_3 to remove the *m*-chlorobenzoic acid. The product is isolated by removal of the solvent and is purified by chromatography on silica gel.

4450

Example 14B

4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 14A is hydrolyzed according to the procedure of Example 6C to give the title acid.

4455

Example 14C

4-(2-pyridylsulfonyl)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 14B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

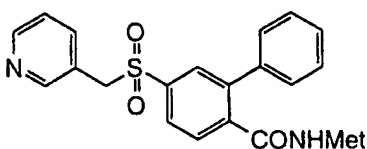
4460

Example 14D

4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

The resultant compound from Example 14C is hydrolyzed according to the procedure of Example 1B to give the title product.

4465

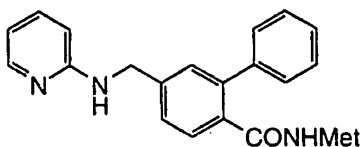


Example 15

4470

4-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

The title compound is prepared from the resultant product of Example 12B using the procedures from Example 14.



4475

Example 16

4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

4480

Example 16A2-Phenylterephthalic acid mono methyl ester

A solution of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), Pd(OAc)₂ (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

4485

Example 16B4-(Hydroxymethyl)-2-phenylbenzoic acid methyl ester

The resultant acid from Example 16A (1.0 equivalent) is treated with a slight excess of N-methylmorpholine (1.1 equivalent) and isobutylchloroformate (1.0 equivalent) in THF at 0° C. The mixture is then treated with NaBH₄ (1.0 equivalent) and aqueous NaHCO₃ and stirred at 0° C until the reaction is judged complete by TLC analysis. The mixture is poured into dilute aqueous acid and extracted into ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

4495

Example 16C4-(Hydroxymethyl)-2-phenylbenzoic acid

The resultant compound from Example 16B is hydrolyzed according to the procedure of Example 6C to give the title acid.

4500

Example 16D4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester

The resultant product from Example 16C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

4505

Example 16E4-formyl-2-phenylbenzoyl methionine methyl ester

A mixture of the resultant alcohol from Example 16D (1.0 equivalent), N-methylmorpholine-N-oxide (1.5 equivalents), molecular sieves, and a catalytic amount of TPAP is stirred in a CH₂Cl₂/acetonitrile mixture until the reaction is judged complete by TLC analysis. The mixture is diluted with ethyl ether and filtered through SiO₂. The product is purified by chromatography on silica gel.

4515

Example 16F4-(formyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

A mixture of (2-phenyl-4-bromobenzoyl) methionine methyl ester (100 mmol), 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (100 mmol), tetrakis(triphenylphosphine)palladium (0) (3 mmol) in toluene and 2 M sodium carbonate in water (100 mL) is heated at 80 °C until the starting methyl ester disappears. The resulting mixture is extracted with ether, and washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. To a solution of the resulting vinyl compound in dioxane/water (4/1) is added osmium tetraoxide (0.03 equivalent), N-methylmorpholine N-oxide (3 equivalents), and the reaction is stirred at 25 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to afford the title product.

Example 16G4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

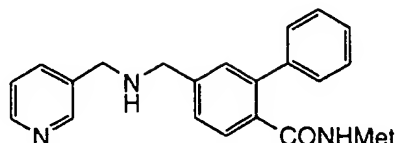
To a solution of the resultant compound from Example 16E in ethanol at 0 °C is added sodium borohydride (0.5 equivalent), and the reaction is stirred at 0 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to afford the title product.

Example 16H4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant aldehyde from Example 16E (1.0 equivalent), 2-aminopyridine (1.0 equivalent) and NaCNBH₃ (1.5 equivalents) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous NaHCO₃ and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 16I4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

The resultant compound from Example 16H is hydrolyzed according to the procedure of Example 1B to give the title product.

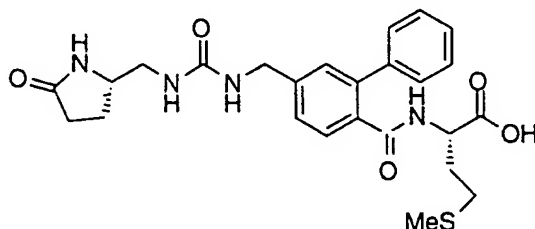


4560

Example 174-[(3-aminomethylpyridyl)methylene]-2-phenylbenzoylmethionine

Using the procedures of Examples 16F-G and replacing 2-aminopyridine with 3-aminomethylpyridine affords the title product.

4565

Example 184-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

4570

Example 18A4-(Azidomethyl)-2-phenylbenzoyl methionine methyl ester

To triphenylphosphine (1.0 equivalent) in tetrahydrofuran (THF) at -78°C is added diethyl azodicarboxylate (1.0 equivalent) in THF. To this mixture is added a solution of hydrazoic acid in benzene (2.0 equivalents) and then the resultant compound from Example 16D (1.0 equivalent). After one hour the mixture was warmed to room temperature, stirred until the reaction is judged complete by TLC analysis, evaporated and chromatographed on silica gel to afford the title product.

4580

Example 18B4-(Aminomethyl)-2-phenylbenzoyl methionine methyl ester

To the resultant compound from Example 18A in methanol is added triethylamine (3.0 equivalent) and propane 1,3-dithiol (3.0 equivalents). After the reaction is judged complete

by TLC analysis, the mixture is filtered and evaporated. Chromatography of the residue on
 4585 silica gel provides the title product.

Example 18C

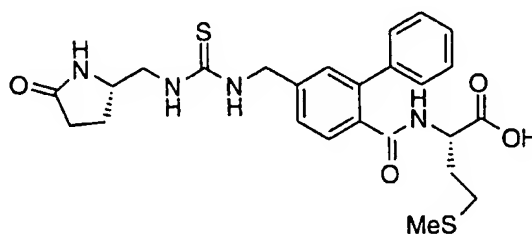
4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine methyl ester

4590 To a solution of the resultant compound from Example 18B (1.0 equivalent) in methylene
 chloride is added triphosgene (0.33 equivalent) and triethyl amine (2.0 equivalents). This
 intermediate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone
 (1.0 equivalent) and triethylamine (1.0 equivalent). When judged complete by TLC
 analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine,
 4595 evaporated, and purified by chromatography on silica gel.

Example 18D

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

The resultant compound from Example 18C is hydrolyzed according to the procedure of
 4600 Example 1B to give the title product.



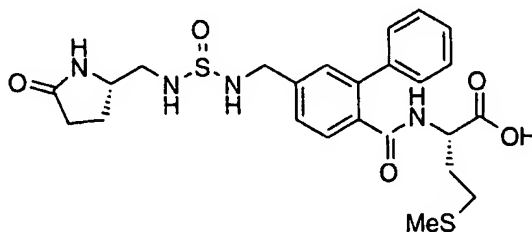
4605

Example 19

4-((S)-2-Pyrrolidone-5-aminomethylthiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

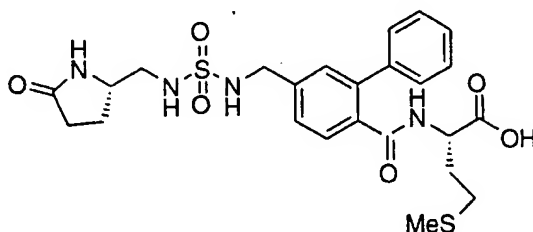
The title compound is prepared as described in Example 18 with the exception that
 triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

4610



Example 204-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)aminomethyl-2-phenylbenzoyl methionine

4615 The title compound is prepared as described in Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent).

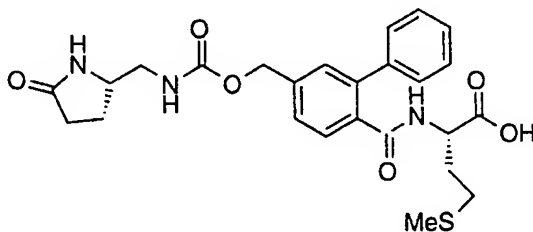


4620

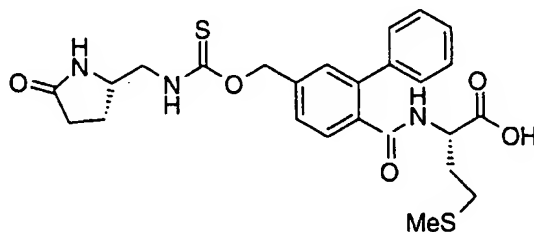
Example 214-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)aminomethyl-2-phenylbenzoyl methionine

Using the Procedure of Example 4 with the resultant compound from Example 18B affords the title product.

4625

Example 224-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxymethylene)-2-phenylbenzoyl methionine

Using the procedure of Example 8 with the resultant compound from Example 16D provides the title product.

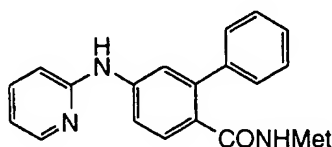


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Example 23

4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxymethylene)-2-phenylbenzoyl
methionine

Using the procedure of Example 8 with the resultant compound from Example 16D and replacing triphosgene (0.33 equivalent) with thiophosgene (1.0 equivalent) provides the title product.



Example 24

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

Example 24A

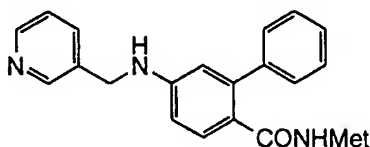
4-(2-Aminopyridyl)-2-phenylbenzoylmethionine methyl ester

4-Amino-2-phenylbenzoyl methionine (1.0 equivalent) methyl ester and 2-bromopyridine hydrobromide (1.0 equivalent) in pyridine are heated until the reaction is judged complete by TLC analysis. The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 24B

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

The resultant compound from Example 24A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 25

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

Example 25A

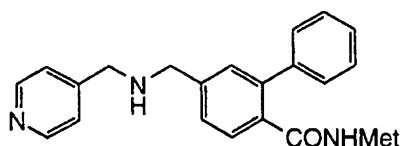
4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine methyl ester

A mixture of 3-pyridinecarboxaldehyde (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and NaCNBH₃ (1.0 equivalent) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous NaHCO₃ and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 25B

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

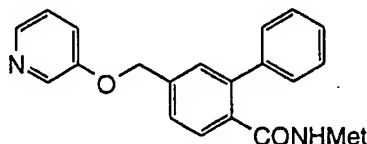
The resultant compound from Example 25A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 26

4-[(4-aminomethylpyridyl)methylene]-2-phenylbenzoylmethionine

Using the procedures of Examples 25 with the resultant amine from Example 18B and 3-pyridinecarboxaldehyde affords the title product.



Example 27

4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

Example 27A

4-(p-Toluenesulfonyloxy)-2-phenylbenzoylmethionine methyl ester

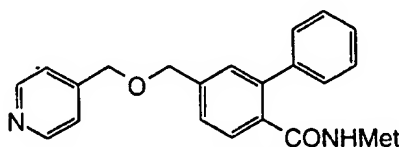
The resultant compound from Example 16D (1.0 equivalent) and *p*-toluenesulfonyl chloride (1.0 equivalent) in pyridine are stirred until the reaction is judged complete by TLC analysis. The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 27B4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine methyl ester

3-Hydroxypyridine (1.0 equivalent) is treated with sodium hydride (1.0 equivalent) in DMSO, then the resultant compound from Example 27A (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

Example 27C4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

The resultant compound from Example 27B is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 284-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionineExample 28A4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

Using the procedure of Example 27B but replacing 3-hydroxypyridine with 3-hydroxymethylpyridine affords the title compound.

Example 28B4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester, alternate procedure

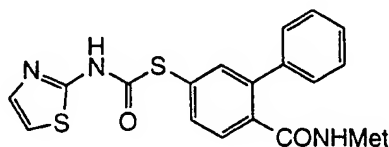
The resultant compound from Example 16D (1.0 equivalent) is treated with sodium hydride (2.0 equivalents) in DMSO, then 3-chloromethylpyridine hydrochloride (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

Example 28C

4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

The resultant compound from Example 28A is hydrolyzed according to the procedure of

4735 Example 1B to give the title product.

Example 29

4740 {2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine

Example 29AThiazol-2-ylisocyanate

A solution of 2-aminothiazol (1.0 mmol), triphosgene (0.34 mmol) and triethylamine (1.0
4745 mmol) in toluene (10 mL) is refluxed until TLC shows no starting amine left. The solvent is then removed in vacuo, and the resulting material is used without further purification.

Example 29B{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine methyl ester

4750 A solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or 12F (1.0 mmol) and the isocyanate prepared in example 29A (1.0 mmol) in THF is refluxed until TLC shows no thiol left. The solvent is then evaporated in vacuo, and the residue is purified by column chromatography on silica gel to give the title compound.

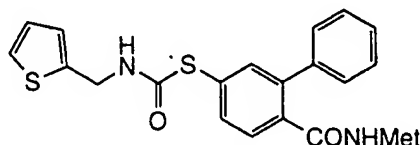
4755 Example 29C

{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine methyl ester, alternate procedure

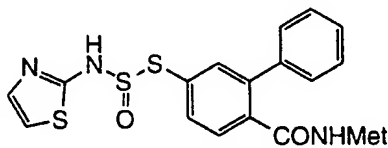
To a solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or 12F (1 equivalent) in methylene chloride is added a solution of phosgene in toluene (1.0
4760 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged complete by TLC analysis, the solvent is evaporated with toluene chasers. The thiochloroformate is reacted without further purification with 2-aminothiazol (1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and
4765 brine, evaporated, and purified by chromatography on silica gel.

Example 29D{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine

The resultant compound from Example 29B is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 30{2-Phenyl-4-[(thien-2-ylmethylamino)carbonylthio]benzoyl}-methionine

Using the procedure of Example 29 but replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

Example 31{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionineExample 31A(N-Thionyl)thiazol-2-ylamine

A solution of 2-aminothiazol (1.0 mmol), in thionyl chloride is heated at reflux until the reaction is judged to be complete by TLC analysis. Then, the excess thionylchloride is distilled out in vacuo. The resulting material is used without further purification.

Example 31B{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester

Using the procedure of Example 29B but replacing the resultant product from Example 29A with the resultant product from Example 31A affords the title compound.

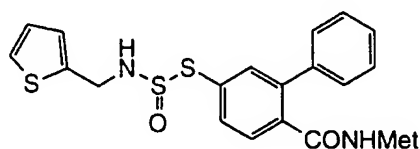
Example 31C{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester, alternate procedure

Using the procedure of Example 29C but replacing phosgene in toluene with thionyl
chloride affords the title compound.

Example 31D

{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine

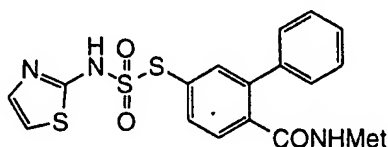
The resultant compound from Example 31B is hydrolyzed according to the procedure of
Example 1B to give the title product.



Example 32

{2-Phenyl-4-[(thien-2-ylmethylamino)thionylthio]benzoyl}-methionine

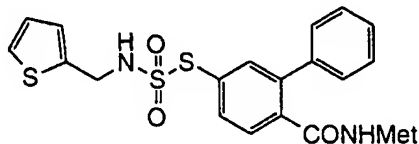
Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 33

{2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthio]benzoyl}-methionine methyl ester

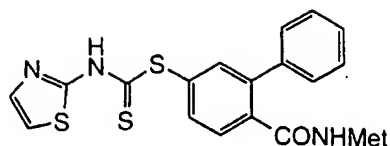
Using the procedure of Example 31 but replacing thionyl chloride with sulfonyl chloride
affords the title product.



Example 34

{2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthio]benzoyl}-methionine

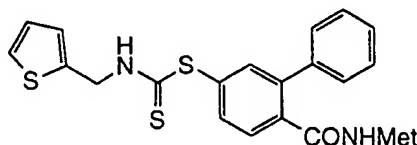
Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-ylmethylamine and replacing thionyl chloride with sulfonyl chloride affords the title product.



Example 35

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthio]benzoyl}-methionine

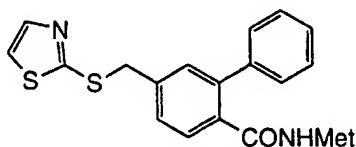
Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.



Example 36

{2-Phenyl-4-[(thien-2-ylmethylamino)thiocarbonylthio]benzoyl}-methionine

Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 37

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine

Example 37A

[2-Phenyl-4-[thiomethyl]benzoyl]-methionine methyl ester

The resultant product from Example 27A is dissolved DMF/water (2/1), and sodium hydrosulfide (5 equivalent) is added to the reaction mixture. The reaction is stirred until TLC analysis shows that the reaction is complete. Then, the reaction mixture is acidified with 3 N HCl to about pH 4, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified with column chromatography on silica gel to give the title compound.

Example 37B

{2-Phenyl-4-[thiomethyl]benzoyl}-methionine methyl ester, alternate procedure

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 16D (1. equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

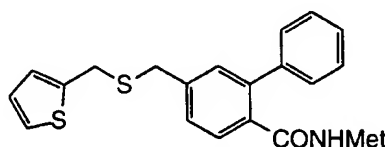
Example 37C

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine methyl ester

A mixture of the resultant thiol from Example 37A (1 mmol), 2-bromothiazole (1.5 mmol), and anhydrous potassium carbonate (5 mmol) in DMF is stirred at 100 °C until TLC analysis shows that the starting thiol disappeared. Then, the reaction mixture is diluted with water, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified by column chromatography on silica gel to give the title compound.

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine

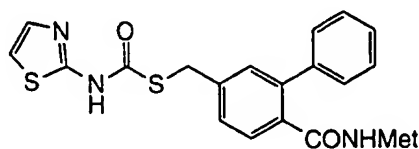
The resultant compound from Example 37C is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 38

{2-Phenyl-4-[(thien-2-yl)methyl]thiomethyl]benzoyl}-methionine

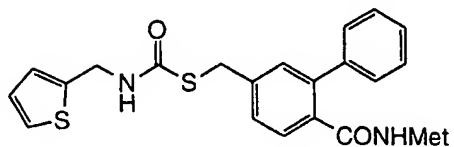
Using the procedure of Example 37 and replacing 2-bromothiazole with 2-bromomethylthiophene affords the title product.



Example 39

4890 {2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 29 with the resultant product from Example 37A affords the title product.



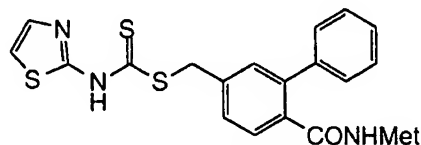
4895

Example 40

{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 29 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

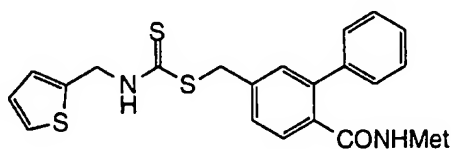
4900



Example 41

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

4905 Using the procedure of Example 29 with the resultant product from Example 37A and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.



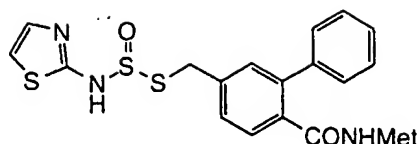
4910

Example 42

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 29 with the resultant product from Example 37A, replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol), and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4915

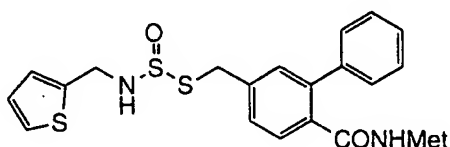


4920

Example 43{2-Phenyl-4-[(thiazol-2-ylamino)thionylthiomethyl]benzoyl}-methionine

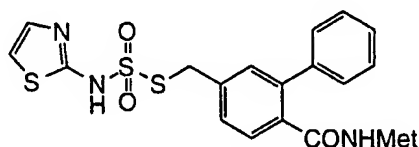
Using the procedure of Example 31 with the resultant product from Example 37A affords the title product.

4925

Example 44{2-Phenyl-4-[(thien-2-ylmethylamino)thionylthiomethyl]benzoyl}methionine

Using the procedure of Example 31 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4930

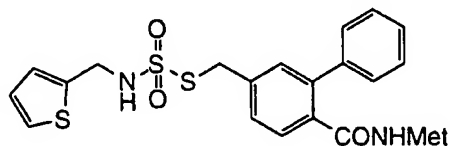
Example 45

4935

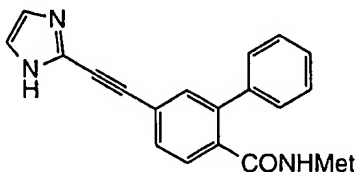
{2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 31 with the resultant product from Example 37A and replacing thionyl chloride with sulfonyl chloride affords the title product.

4940

Example 46{2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 31 with the resultant product from Example 37A, replacing thionyl chloride with sulfonyl chloride, and replacing 2-aminothiazol with thien-2-ylmethylaniline affords the title product.



Example 47

{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}-methionine

Example 47A

(4-Ethynyl-2-phenylbenzoyl)-methionine methyl ester

A mixture of (2-phenyl-4-bromobenzoyl)-methionine methyl ester (100 mmol), diethylamine (300 mmol), trimethylsilylacetylene (110 mmol), bis(triphenylphosphine) palladium diacetate (5 mmol) and copper(I) iodide (3 mmol) in toluene is heated at 60 °C until TLC analysis indicates the starting methyl ester has disappeared. The reaction mixture is concentrated in vacuo, redissolved in ether, filtered through silica gel, and concentrated.

The residue is then dissolved in THF, and is treated with tetrabutylammonium fluoride (120 mmol). After TLC analysis indicates that no starting material is left, the reaction mixture is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified with column chromatography on silica gel to give the title product.

Example 47B

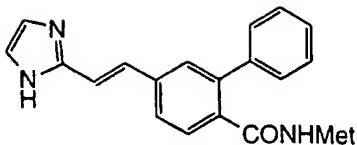
{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}-methionine methyl ester

The resultant product from Example 47A (5 mmol) is mixed with 4-bromoimidazole (5 mmol), diethylamine (1 mL), bis(triphenylphosphine) palladium diacetate (0.1 mmol) and copper(I) iodide (0.1 mmol) in toluene. The mixture is stirred at 25 °C until TLC analysis indicates the reaction is complete. The reaction mixture is concentrated in vacuo, and the residue is purified with column chromatography on silica gel to give the title product.

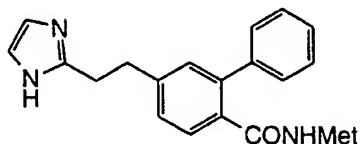
Example 47C

{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}-methionine

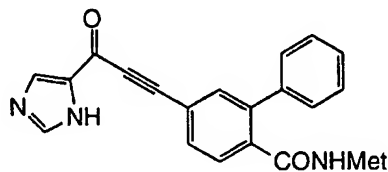
The resultant compound from Example 47B is hydrolyzed according to the procedure of Example 1B to give the title product.

**Example 48****{4-[2-(Imidazol-4-yl)ethenyl]-2-phenylbenzoyl}-methionine**

The resultant acetylene (3 mmol) from Example 47 is mixed with Lindlar catalyst (50 mg), 5 drops of quinoline in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.

**Example 49****{4-[2-(Imidazol-4-yl)ethyl]-2-phenylbenzoyl}-methionine**

The resultant olefin (1 mmol) from Example 48 is mixed with 5% palladium on carbon (100 mg) in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.

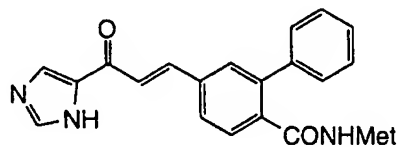
**Example 50****{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine****Example 50A****{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine methyl ester**

A stainless autoclave containing the resultant product from Example 47A (5 mmol), 4-bromoimidazole (5 mmol), 1,1'-bis(diphenylphosphine)-ferrocenepalladium dichloride (0.1 mmol), and triethylamine (10 mL) is flushed with nitrogen, and pressurized to 20 atm with carbon monoxide. The reaction mixture is stirred at 120 °C until judged complete by TLC analysis. After cooling, the triethylamine is evaporated in vacuo, and the residue is purified by column chromatography on silica gel to give the title compound.

Example 50B

{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine

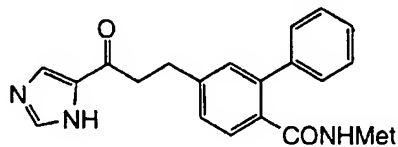
The resultant compound from Example 50A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 51

{4-[2-(Imidazol-4-ylcarbonyl)ethenyl]-2-phenylbenzoyl}-methionine

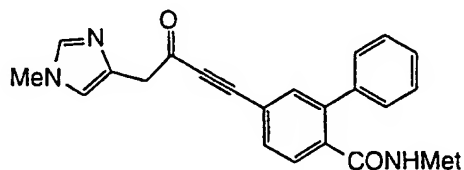
Using the procedure of Example 48 with the resultant compound from Example 50 affords the title product.



Example 52

{4-[2-(Imidazol-4-ylcarbonyl)ethyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 49 with the resultant compound from Example 51 affords the title product.



Example 53

5035 {4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine

Example 53A

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine methyl ester

5040 To a solution of 1-methyl-4-imidazoleacetic acid (5 mmol) in methylene chloride at 0 °C is added oxalyl chloride (6 mmol) and DMF (0.05 mmol). After 30 minute, the solvent is evaporated in vacuo. The residue is redissolved in dichloromethane, followed by the addition of the resultant acetylene from Example 47A (5 mmol), triethylamine (10 mmol), and copper(I) iodide (1 mmol). The reaction is stirred at 25 °C until TLC analysis indicates

5045 no starting material is left in the reaction mixture. The reaction is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to give the title compound.

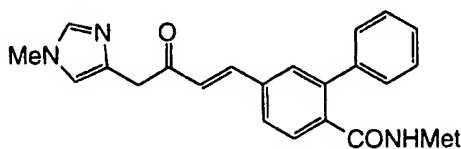
5050

Example 53B

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine

The resultant compound from Example 53A is hydrolyzed according to the procedure of Example 1B to give the title product.

5055

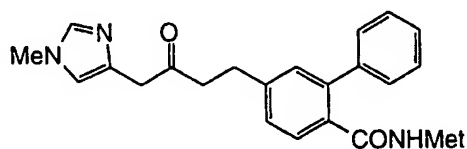


Example 54

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butenyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 48 with the resultant compound from Example 53 affords

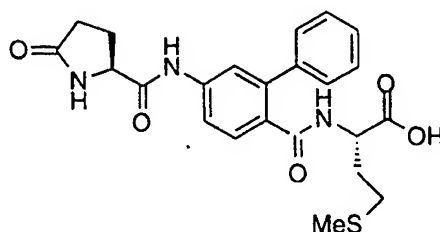
5060 the title product.



Example 55

5065 {4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 49 with the resultant compound from Example 53 affords the title product.



Example 56

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

Example 56A

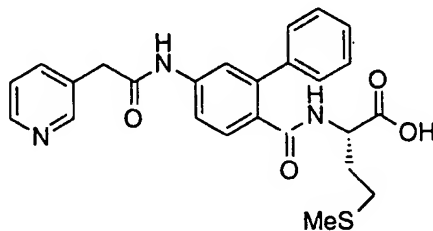
(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine methyl ester

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 56B

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

The resultant compound from Example 56A is hydrolyzed according to the procedure of Example 1B to give the title product.

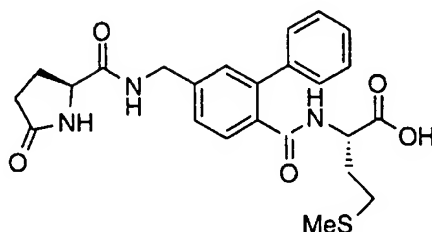


Example 57

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

Using the procedure of Example 56 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.

5095

Example 58

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

5100

Example 58A

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine methyl ester

To a solution of the resultant amine from Example 18B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

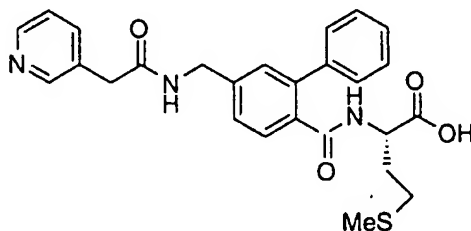
5110

Example 58B

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

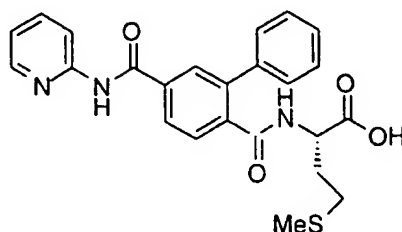
The resultant compound from Example 58A is hydrolyzed according to the procedure of Example 1B to give the title product.

5115

Example 59

naming error(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

- 5120 Using the procedure of Example 58 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.



5125

Example 60

4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

Example 60A

4-Carboxy-2-phenylbenzoyl methionine methyl ester

- 5130 A solution of 4-bromo-2-phenylbenzoyl methionine methyl ester (1.0 equivalent), Pd(OAc)₂ (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

5135

Example 60B

4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine methyl ester

- 5140 To a solution of the resultant acid from Example 60A (1.0 equivalent) in DMF is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

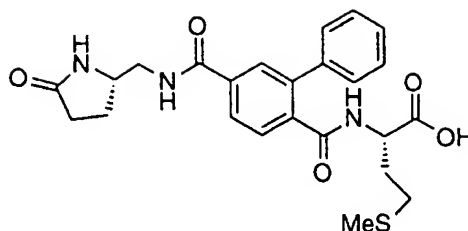
5145

Example 60C

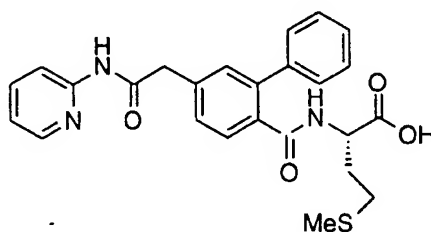
4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

- The resultant compound from Example 60B is hydrolyzed according to the procedure of Example 1B to give the title product.

5150

Example 614-((S)-2-Pyrrolidone-5-aminomethyl)carbonyl-2-phenylbenzoyl methionine

Using the procedure of Example 60 and replacing 2-aminopyridine with (S)-5-aminomethyl-2-pyrrolidone affords the title product.

Example 624-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionineExample 62A4-Diazocarbonyl-2-phenylbenzoyl methionine methyl ester

The resultant acid from Example 60A (1 equivalent) in dichloromethane is treated with oxalyl chloride (1 equivalent) and DMF (0.05 equivalent). When gas evolution has ceased, the acid chloride solution is added to an ether solution of diazomethane. The reaction is stirred until judged complete by TLC analysis, and then is concentrated to give the crude title compound which is purified by chromatography on silica gel.

Example 62B4-carboxymethyl-2-phenylbenzoyl methionine methyl ester

The resultant compound from Example 62A (1 equivalent) in dioxane is added to a slurry of sodium thiosulfate (1.1 equivalents) and silver (I) oxide (0.5 equivalent) in water. The reaction is stirred until judged complete by TLC analysis, filtered, acidified, and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title product.

Example 62C

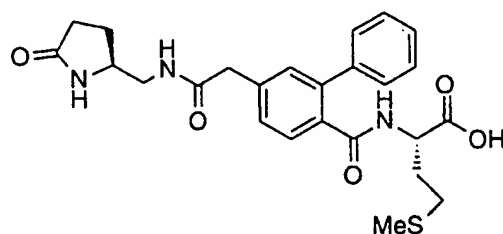
4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine methyl ester

5180 To a solution of the resultant acid from Example 62B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried

5185 and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 62D4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine

5190 The resultant compound from Example 62C is hydrolyzed according to the procedure of Example 1B to give the title product.

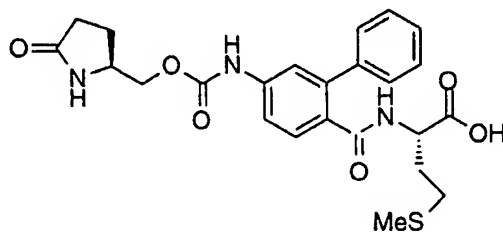


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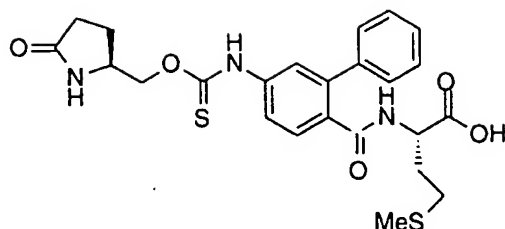
Example 634-((S)-2-Pyrrolidone-5-aminomethyl)carbonylmethyl-2-phenylbenzoyl methionine

Using the procedure of Example 62 and replacing 2-aminopyridine with (S)-5-aminomethyl-2-pyrrolidone affords the title product.

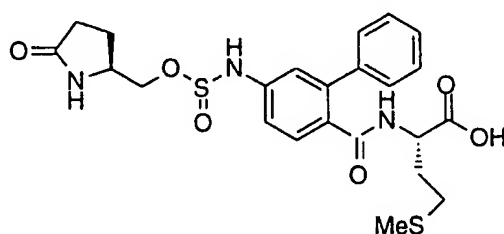
5200

Example 644-((S)-2-Pyrrolidone-5-methoxycarbonyl)amino-2-phenylbenzoyl methionine

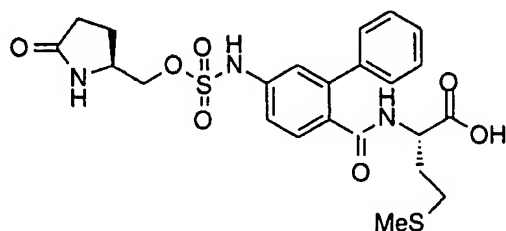
5205 The title compound is prepared as described in Example 1 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

Example 654-((S)-2-Pyrrolidone-5-methoxythiocarbonyl)amino-2-phenylbenzoyl methionine

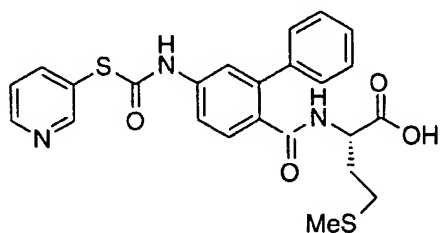
The title compound is prepared as described in Example 1 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

Example 664-((S)-2-Pyrrolidone-5-methoxysulfonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 3 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

Example 674-((S)-2-Pyrrolidone-5-methoxysulfonyl)amino-2-phenylbenzoyl methionine

5230 The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

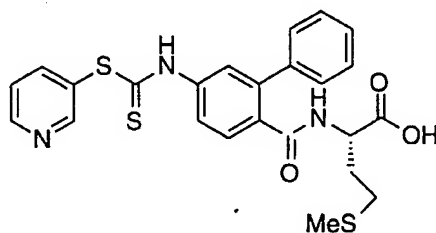


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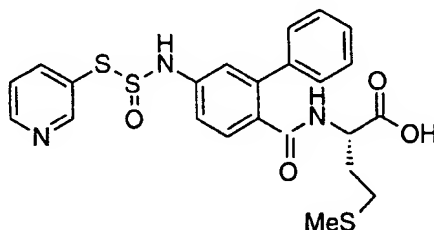
Example 684-(Pyridin-3-ylmercaptocarbonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5240

Example 694-(Pyridin-3-ylmercaptothiocabonyl)amino-2-phenylbenzoyl methionine

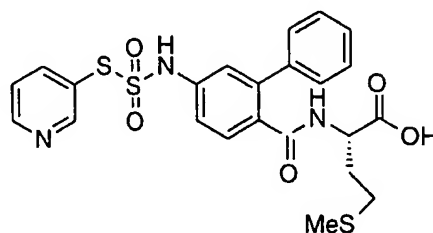
5245 The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



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Example 704-(Pyridin-3-ylmercaptosulfinyl)amino-2-phenylbenzoyl methionine

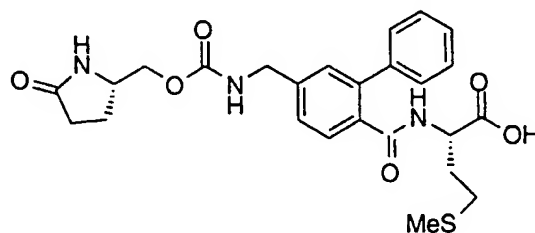
The title compound is prepared as described in Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 71

4-(Pyridin-3-ylmercaptosulfonyl)amino-2-phenylbenzoyl methionine

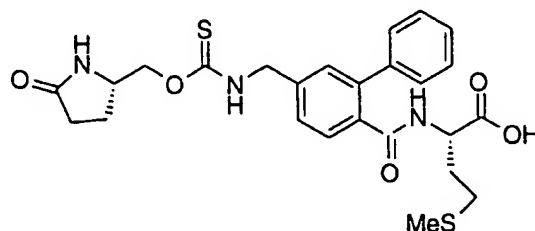
The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 72

4-((*S*)-2-Pyrrolidone-5-methoxycarbonyl)aminomethyl-2-phenylbenzoyl methionine

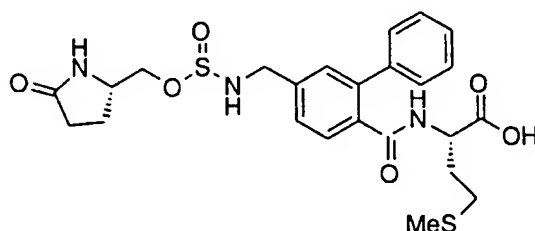
The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 73

4-((*S*)-2-Pyrrolidone-5-methoxythiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

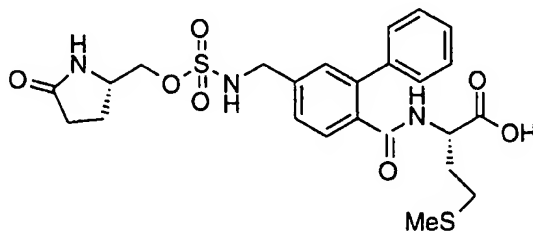
The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



Example 74

4-((*S*)-2-Pyrrolidone-5-methoxysulfinyl)aminomethyl-2-phenylbenzoyl methionine

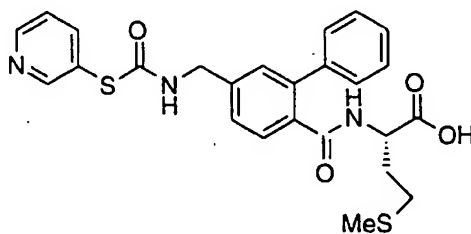
The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 75

4-((*S*)-2-Pyrrolidone-5-methoxysulfonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

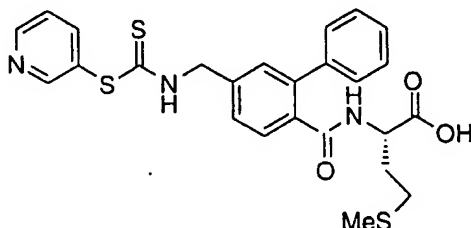


Example 76

4-(Pyridin-3-ylmercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

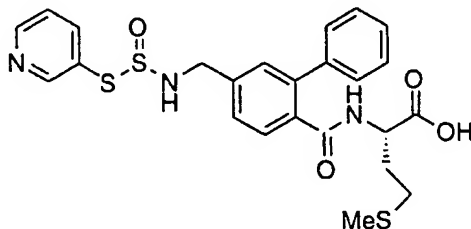
The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

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Example 774-(Pyridin-3-ylmercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

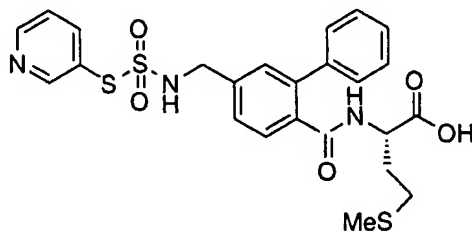
The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

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Example 784-(Pyridin-3-ylmercaptosulfinyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

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Example 79

5325 4-(Pyridin-3-ylmercaptosulfonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5330

Example 80A-NH-CO-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

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Example 81A-NH-CS-NH-B

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The procedure of Example 1 is used with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

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5355

Example 82A-NH-SO-NH-B

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-

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aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5365 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5370

Example 83

A-NH-SO₂-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and
5375 (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
5380 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

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Example 84

A-NH-SO₂-B

The procedure of Example 5 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products
5390 derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
5395 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 85

A-NH-CO-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E.

5400 The resultant phenols are reacted according to the procedure of Example 8 with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5405 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5410

Example 86

A-NH-CS-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thiophosgene and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5420 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5425

Example 87

A-NH-SO-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5430 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

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Example 88A-NH-SO₂-O-B

5440 The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by sulfuryl chloride and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes
5445 the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5450

Example 89A-NH-CH₂-B

The procedure of Example 16 is used with the exception that (2-phenyl-4-bromobenzoyl)-methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine
5455 is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5460

Example 90A-NH-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from
5470 Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 91

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A-NH-CS-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 92

A-NH-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 93

A-NH-SO₂-NH-CH₂-B

5510 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by sulfuryl chloride (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also
5515 hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl,
5520 butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 94

A-NH-CO-O-CH₂-B

5525 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from
5530 amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5535

Example 95

A-NH-CS-O-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the
5540 exception that phosgene in toluene is replaced by thiophosgene and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
5545 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 96

A-NH-CO-S-B

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The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5555

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5560

Example 97

A-NH-CS-S-B

5565

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5570

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

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Example 98

A-NH-SO-S-B

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The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from

amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5585 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5590

Example 99

A-NH-SO₂-S-B

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of
5595 Example 29 with the exception that phosgene in toluene is replaced by sulfuryl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
5600 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5605

Example 100

A-NH-CO-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the
5610 procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
5615 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

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Example 101A-NH-CS-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

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This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

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Example 102A-NH-SO-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

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This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5650

Example 103A-NH-SO₂-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by sulfuryl

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chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5660 example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5665

Example 104A-CO-NH-B

The procedure of Example 56 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and pyroglutamic acid is replaced by an acid from Table 4 (A-CO₂H). For products derived from acids 164-
5670 238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

5675 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

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Example 105A-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the
5685 procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 58 with the exception that pyroglutamic acid is replaced by an acid from Table 4 (A-CO₂H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of
5690 dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 106

A-CO-C \equiv C-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 47A. The resultant acetylenes are reacted according to the procedure of Example 53 with the exception that 1-methyl-4-imidazoleacetic acid is replaced by an acid from Table 4 (A-CO₂H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 107

A-CO-CH=CH-B

The products from Example 106 are reacted according to the procedure of Example 54. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 108

A-CO-CH₂-CH₂-B

The products from Example 107 are reacted according to the procedure of Example 55. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

5730 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 109

5735

A-NH-CO-B

5740

The procedure of Example 60 is used with the exception that 4-bromo-2-phenylbenzoyl methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5745

Example 110

A-NH-CO-CH₂-B

5750

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 60A. The resultant carbocyclic acids are reacted according to the procedure of Example 62 with the exception that 2-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5755

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5760

Example 111

A-CH₂-NH-B

5765

The procedure of Example 25 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an amine from Table 1 (B-NH₂) and 3-pyridinecarboxaldehyde is replaced by an aldehyde from Table 5 (A-CHO). For products derived from aldehydes 360-432 and 433-440 from Table 5, the LiOH hydrolysis step is

followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

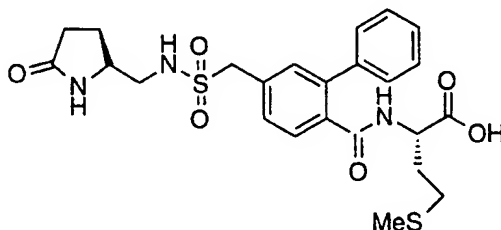
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 112

A-CH₂-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 25 with the exception that 3-pyridinecarboxaldehyde is replaced by an aldehyde from Table 5 (A-CHO). For products derived from aldehydes 360-432 and 433-440 from Table 5, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



Example 113

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethyl)-2-phenylbenzoyl methionine

Example 113A5800 4-Thioacetoxymethyl-2-phenylbenzoic acid methyl ester

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thioacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 16B (1. equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

5810

Example 113B4-Chlorosulfonylmethylene-2-phenylbenzoic acid methyl ester

The resultant compound from Example 113A in water is stirred vigorously while gaseous chlorine is bubbled through the mixture. When the reaction is judged to be done by TLC analysis, the reaction is extracted with dichloromethane which is dried and evaporated to afford the title product.

Example 113C4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoic acid methyl ester

To a solution of the resultant compound from Example 113B (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

5825

Example 113D4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoic acid

The resultant compound from Example 113C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 113E5830 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 113D (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged

complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

5840

Example 113F4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl methionine

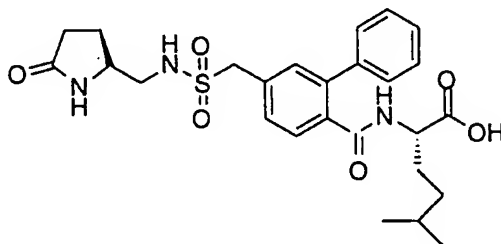
The resultant compound from Example 113E is hydrolyzed according to the procedure of Example 1B to give the title product.

5845

Example 114A-NH-SO₂-CH₂-B

The procedure of Example 113 is used with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5850



5855

Example 1154-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethyl-2-phenylbenzoyl leucineExample 115A4-(Hydroxymethyl)-2-phenylbenzoyl leucine methyl ester

(2-phenyl-4-bromobenzoyl)-leucine methyl ester is reacted according to the procedures of Example 16F-G.

5860

Example 115B4-Thioacetoxymethyl-2-phenylbenzoyl leucine methyl ester

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thioacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 115A (1. equivalent) in THF. The

5865

reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

Example 115C

4-Chlorosulfonylmethylene-2-phenylbenzoyl leucine methyl ester

The resultant compound from Example 115B in water is stirred vigorously while gaseous chlorine is bubbled through the mixture. When the reaction is judged to be done by TLC analysis, the reaction is extracted with dichloromethane which is dried and evaporated to afford the title product.

Example 115D

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl leucine methyl ester

To a solution of the resultant compound from Example 115C (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

Example 115E

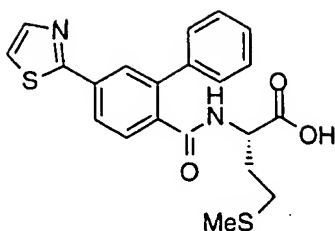
4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl leucine

The resultant compound from Example 115D is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 116

A-NH-SO₂-CH₂-B

The procedure of Example 115 is used with the exception that (2-phenyl-4-bromobenzoyl)-leucine methyl ester is replaced by a bromide from Table 2, entries 28-132 (B-Br) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.



5905

Example 1174-(2-Thiazolyl)-2-phenylbenzoyl methionineExample 117A2-Thiazole boronic acid

5910 A solution of thiazole (1.0 equivalent) is lithiated with a slight excess of n-butyl lithium in THF (1.05 equivalents) and then treated with trimethyl borate (1.05 equivalents). The reaction mixture is quenched by the addition of aqueous HCl and the resulting boronate ester is cleaved by the addition of excess aqueous NaOH. After acidification and extraction into ethyl acetate the crude boronic acid is used without further purification.

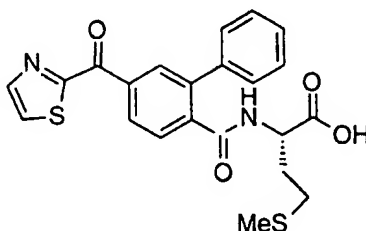
5915

Example 117B4-(2-Thiazolyl)-2-phenylbenzoyl methionine methyl ester

A mixture of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), 2-thiazole boronic acid (1.0 equivalent) and catalytic Pd(PPh₃)₄ is heated in a two phase system of
 5920 toluene and aqueous Na₂CO₃. After cooling, the resulting biaryl compound is isolated by evaporation of the organic phase and is purified by chromatography on silica gel.

Example 117C4-(2-Thiazolyl)-2-phenylbenzoyl methionine

5925 The resultant compound from Example 117C is hydrolyzed according to the procedure of Example 1B to give the title product.



5930

Example 1184-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine

Example 118A4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine methyl ester

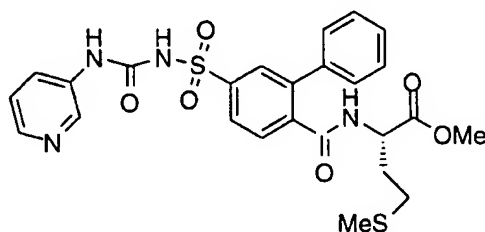
5935 A mixture of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), 2-thiazole boronic acid from Example 117A (1.0 equivalent) and catalytic $\text{Pd}(\text{PPh}_3)_4$ is heated in a two phase system of toluene and aqueous Na_2CO_3 previously purged with a large excess of carbon monoxide. The resulting diaryl ketone is isolated by evaporation of the organic phase and is purified by chromatography on silica gel.

5940

Example 118B4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine

The resultant compound from Example 118A is hydrolyzed according to the procedure of Example 1B to give the title product.

5945

Example 1194-[(3-Aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine

5950

Example 119A4-Aminosulfonyl-2-phenylbenzoylmethionine methyl ester

To a solution of 4-chlorosulfonyl-2-phenylbenzoyl methionine methyl ester from Example 5E in dichloromethane is added aqueous ammonia and the mixture is stirred until the reaction is judged complete by TLC analysis. The organic phase is separated, dried and evaporated and the product is purified by chromatography on silica gel.

5955

Example 119B4-Isocyanatosulfonyl-2-phenylbenzoylmethionine methyl ester

5960 A mixture of the resultant sulfonamide from Example 119A in chlorobenzene is treated with oxalyl chloride according to the procedure of Franz et al. (*J. Org. Chem.*, 1964, 29, 2592) to give the title compound.

Example 119C

5965 4-[(A-aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant isocyanate from Example 119B (1 equivalent) in dichloromethane is treated with 3-aminopyridine (1 equivalent) and stirred until the reaction is judged complete by tlc analysis. The solvent is evaporated and the product is purified by chromatography on silica gel.

5970

Example 119D

4-[(A-aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine

The resultant compound from Example 119C is hydrolyzed according to the procedure of Example 1B to give the title product.

5975

Example 120

A-NH-CO-NH-SO₂-B

5980 The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Example 5E to afford the corresponding sulfonyl chlorides. These are reacted according to the procedure of Example 119 with the exception that 3-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5985 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5990

Example 121

A-NH-CO-NH-SO₂-CH₂-B

5995 The bromides from Table 2, entries 28-132 (B-Br) are reacted according to the procedures of Example 115A-C to afford the corresponding sulfonyl chlorides. These are reacted according to the procedure of Example 119 with the exception that 3-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

6000 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 122

A-O-CH₂-B

6005 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 27 with the exception that 3-hydroxypyridine is replaced by an alcohol from Table 6 (A-OH). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by
6010 stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
6015 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 123

A-O-CO-NH-B

6020 The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359
6025 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6030 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 124

A-O-CS-NH-B

6035

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂), (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 125

A-O-SO-NH-B

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 126

A-O-SO₂-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH,

1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359
6075 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butylloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6080 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6085

Example 127

A-O-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the
6090 exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butylloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and
6095 trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
6100 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 128

A-O-CS-NH-CH₂-B

6105 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from
6110 alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by

removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6115 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6120

Example 129

A-O-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 3
6125 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane
6130 and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
6135 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 130

A-O-SO₂-NH-CH₂-B

6140 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is
6145 followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane

and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6155

Example 131A-S-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Example 13A. The resultant fluorides are reacted according to the procedure of Example 13 with the exception that 2-mercaptopyridine is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6170

Example 132A-S-CO-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
6185 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 133

A-S-CS-NH-B

6190 The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl
methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂), (S)-5-
aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-
SH), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For
products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is
6195 followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring
the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane
and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The
solvent is evaporated and the residue is purified by chromatography on silica gel.
This example also encompasses compounds comprising a C-terminal ester moiety, in which
6200 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 134

A-S-SO-NH-B

6205 The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl
methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-
aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-
6210 SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis
step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by
stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of
dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is
complete. The solvent is evaporated and the residue is purified by chromatography on silica
6215 gel.
This example also encompasses compounds comprising a C-terminal ester moiety, in which
case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6220

Example 135A-S-SO₂-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 136A-S-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 137A-S-CS-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the

exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH) and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

6260 For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6265 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6270

Example 138

A-S-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 3

6275 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is
6280 complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
6285 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 139

A-S-SO₂-NH-CH₂-B

6290 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting

6295 group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6300 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6305 Example 140

A-O-B

The procedure of Example 6 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 3-bromopyridine is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products
6310 derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6315 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6320

Example 141

A-S-B

The procedure of Example 12 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 2-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products
6325 derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The
6330 solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6335

Example 142

A-NH-B

The procedure of Example 24 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 2-bromopyridine hydrobromide is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6345

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6350

Example 143

A-O-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 28 with the exception that 3-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6360

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6365

6370

Example 144A-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 37 with the exception that 2-bromothiazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I).

6375

For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6380

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6385

Example 145A-C \equiv C-B

The procedure of Example 47 is used with the exception that (2-phenyl-4-bromobenzoyl)-methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 4-

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bromoimidazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6395

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6400

Example 146A-CH=CH-B

The products from Example 145 are reacted according to the procedure of Example 48.

6405 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6410 Example 147
A-CH₂-CH₂-B

The products from Example 146 are reacted according to the procedure of Example 49. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
6415 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6420 Example 148
A-CO-C \equiv C-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 47A. The resultant acetylenes are reacted according to the procedure of Example 50 with the exception that 4-bromoimidazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-230 from Table 8, the LiOH hydrolysis step is
6425 followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety,
6430 in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6435 Example 149
A-CO-CH=CH-B

The products from Example 148 are reacted according to the procedure of Example 48.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to

6440 prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 150

A-CO-CH₂-CH₂-B

6445 The products from Example 149 are reacted according to the procedure of Example 49.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, 6450 butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 151

A-SO₂-B

The anilines from Table 1, entries 28-132 (B-NH₂) are reacted according to the 6455 procedures of Example 13A. The resultant fluorides are reacted according to the procedure of Example 13 with the exception that 2-mercaptopyridine is replaced by a mercaptan from Table 7 (A-SH). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by 6460 stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, 6465 in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 152

A-CH₂SO₂-B

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The procedure of Example 12 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1, entries 28-132 (B-NH₂) and 2-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). The resultant sulfides are oxidized according to the procedure of 6475 Example 14A. For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting

group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 153

A-SO₂-CH₂-B

The bromides from Table 2, entries 28-132 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 37 with the exception that 2-bromothiazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



Example 154

{4-[(3-sulfonylmethyl)pyridyl]amino}-2-phenylbenzoyl}methionine

Example 154A

{4-[(3-sulfonylmethyl)pyridyl]amino}-2-phenylbenzoyl}methionine methyl ester

6510 A mixture of 3-chlorosulfonylmethylpyridine hydrochloride (1.0 equivalent) and (4-amino-2-phenylbenzoyl)methionine methyl ester (1.0 equivalent) in dichloromethane is treated with triethylamine (2.2 equivalents). When judged complete by TLC analysis, the reaction is diluted with ethyl acetate, and then is washed with pH 4 water, saturated NaHCO₃, and brine. The mixture is dried and concentrated to give the crude title compound which is
6515 purified by chromatography on silica gel.

Example 154B

{4-[(3-sulfonylmethylpyridyl)amino]-2-phenylbenzoyl}methionine

The resultant compound from Example 154A is hydrolyzed according to the procedure of
6520 Example 1B to give the title product.

Example 155

A-CH₂SO₂-NH-B

The procedure of Example 154 is used with the exception that 4-amino-2-phenylbenzoyl
6525 methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 3-chlorosulfonylmethylpyridine hydrochloride is replaced by a sulfonyl chloride from Table 9 (A-SO₂Cl).

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
6530 anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

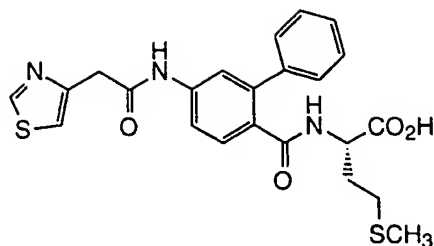
Example 156

A-SO₂-NH-CH₂-B

6535 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 154 with the exception that -chlorosulfonylmethylpyridine hydrochloride is replaced by a sulfonyl chloride from Table 9 (A-SO₂Cl).

6540 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

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Example 162[4-(thiazol-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine

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Example 162AThioformamide

To a mechanically-stirred solution of formamide (4.0 mL, 100 mmol) in THF (45 mL) was added P₄S₁₀ (4.5 g, 10.1 mmol) while the reaction mixture was maintained at <37 °C using an ice-water bath. The reaction mixture was then stirred for 5.5 hours at ambient temperature. The reaction mixture was filtered through a pad of celite and the filter cake was washed with THF. The filtrate was concentrated in vacuo and then under high vacuum for 4 hours to give thioformamide which was used without further purification.

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Example 162BEthyl 4-bromoacetoacetate

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To a mechanically-stirred solution of ethyl acetoacetate (59 mL, 463 mmol) in ether (75 mL) was added bromine (23.5 mL, 912 mmol) while the reaction temperature was maintained below 23 °C using an ice-water bath. The yellow-orange solution was stirred for 5 hours with cooling and then was stirred overnight at ambient temperature. Ice (60 g) was added and the reaction mixture was extracted with ether. The organic phase was washed twice with aqueous NaHCO₃ saturated with NaCl and once with brine. The ether solution was stirred for 1 day over CaCl₂ and then was filtered through celite. The filter cake was rinsed with dichloromethane. The filtrate was concentrated in vacuo to give ethyl 4-bromoacetoacetate (71.5 g) which was stored in the dark and stabilized with BaCO₃ (300 mg).

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Example 162CEthyl 4-Thiazolylacetate

To a solution in absolute ethanol (18 mL) of ethyl 4-bromoacetoacetate (7.0 mL, 10.4 g, 49.7 mmol), prepared as in Example 162B, was added a solution in absolute ethanol/dioxane/toluene of thioformamide (4 g, 65 mmol), prepared as in Example 162A,

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while the reaction temperature was maintained below 35 °C using an ice-water bath. The reaction mixture was stirred at reflux for 30 minutes, and then was cooled to ambient temperature. The reaction mixture was poured into aqueous 2N HCl (210 mL) and extracted twice with ether. The organic extracts were discarded and the aqueous phase was taken to pH 7-8 with NaHCO₃. The aqueous phase was extracted twice with ether. The ether extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo to give 4.7 g of a dark oil. The oil was distilled at 20 mm Hg to give ethyl 4-thiazolylacetate (2.5 g, bp 111-122 °C) as light-yellow oil.

Example 162D

4-Thiazolylacetic acid

A mixture of ethyl 4-thiazolylacetate (2.4 g, 14 mmol), prepared as in Example 162C, and aqueous 10% NaOH was stirred for 10 minutes at ambient temperature. The reaction mixture was cooled to 0 °C and taken to pH 2-3 with concentrated HCl. The resulting white solid was filtered, washed with water and dried under high vacuum in the presence of P₂O₅ to give 4-thiazolylacetic acid (905 mg).

Example 162E

[4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester

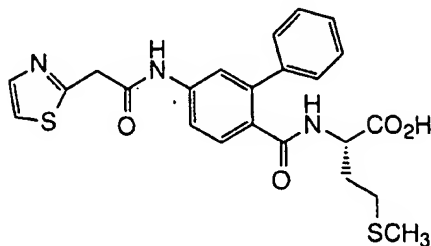
To a suspension in dichloromethane (10 mL) of 4-thiazolylacetic acid (460 mg, 3.22 mmol), prepared as in Example 162D was added oxalyl chloride (300 µL, 3.44 mmol) and DMF (5 mL). The mixture was stirred for 1.5 hours after bubbling ceased, and then was added over 5 minutes to a 5 °C 2-phase mixture of 4-amino-2-phenylbenzoyl methionine methyl ester (compound 8, 1.2 g, 3.2 mmol) in dichloromethane (12 mL) and saturated aqueous NaHCO₃ (15 mL). The cold bath was removed and the reaction mixture was stirred for 1.5 hours. The reaction mixture was partitioned between ethyl acetate and saturated aqueous NaHCO₃. The organic phase was dried over Na₂SO₄, filtered, and concentrated in vacuo to give a dark-brown residue (1.0 g). Chromatography on silica gel (10% ethyl acetate hexane) gave [4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester (581 mg) as a light-yellow powder.

Example 162F

[4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine

The desired compound was prepared by saponification of [4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 162E, using lithium hydroxide hydrate according to the method of Example 159. ¹H NMR (300 MHz, DMSO-d₆) δ 10.42 (s, 1H), 9.06 (d, 1H), 8.43 (d, 1H), 7.70 (d, 1H), 7.63

(dd, 1H), 7.52 (d, 1H), 7.40 (d, 1H), 7.35 (m, 5H), 4.28 (m, 1H), 3.90 (s, 2H), 2.25 (m, 2H), 2.00 (s, 3H), 1.86 (m, 2H); MS (DCI-NH₃) m/e 470 (M+H)⁺. Anal calcd for C₂₃H₂₃N₃O₄S₂: C, 58.83; H, 4.94; N, 8.95. Found: C, 58.44; H, 4.87; N, 8.58.



Example 163

[4-(thiazol-2-yl)methylcarbonyl]amino-2-phenylbenzoyl]methionine

Example 163A

3-bromosuccinaldehydic acid ethyl ester

To a 0-5 °C mechanically-stirred solution in diethyl ether (100 mL) of succinaldehydic acid ethyl ester (10.0 g, 77 mmol) was added bromine (3.9 g, 151 mmol) over 2.5 hours. The reaction mixture was stirred for an additional 1.25 hours and the ether was distilled at atmospheric pressure. The remaining yellow oil was distilled (6.0-6.5 mm Hg, bp 95-101 °C) to give 3-bromosuccinaldehydic acid ethyl ester (10.7 g, 66%).

Example 163B

Ethyl 2-thiazolyl acetate

To a slurry of thioformamide (3.9 g, 64 mmol) in diethyl ether (40 mL) and tetrahydrofuran (15 mL) was added 3-bromo-succinaldehydic acid ethyl ester (10.6 g, 51 mmol), prepared as in Example 163A. The reaction mixture was heated at reflux for 30 minutes, then ethanol (50 mL) was added, 30-40 mL of ether was distilled off, and the reaction mixture was heated at reflux for one hour. The reaction mixture was cooled to ambient temperature and aqueous 2N HCl (200 mL) was added. The mixture was extracted twice with ether. The aqueous phase was taken to pH 7-8 with NaHCO₃ (40 g) and was extracted with ether and twice with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to give an orange oil which was purified by distillation (3 mm Hg, bp 109-111 °C) to give ethyl 2-thiazolyl acetate (2.15 g).

Example 163C

2-Thiazolyl acetic acid

Ethyl 2-thiazolyl acetate (2.35 g, 13.7 mmol), prepared as in Example 163B, was added to 10% aqueous KOH. After about 10 minutes all of the oil dissolved to give a clear, bright-yellow solution. The reaction mixture was cooled to 0 °C and the pH was adjusted to 2-3 using concentrated HCl. The resulting solids were filtered off, rinsed with water, and dried over P₂O₅ under high vacuum to give 2-thiazolyl acetic acid (1.44 g).

Example 163D

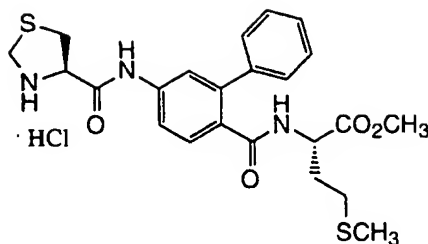
[4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester

To a solution in DMF (4 mL) of 2-thiazolyl acetic acid (300 mg, 2.1 mmol), prepared as in Example 163C, was added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (373 mg, 2.3 mmol) followed by ethyl dimethylaminopropyl carbodiimide hydrochloride (442 mg, 2.3 mmol), and a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (compound 8, 760 mg, 2.0 mmol) in dichloromethane (3 mL) and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with ethyl acetate and washed saturated aqueous NaHCO₃ (2x) and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated in vacuo to give a brown solid (1.12 g). Chromatography on silica gel (ethyl acetate) gave [4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester (600 mg).

Example 163E

[4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine

The desired compound was prepared by saponification of [4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 163D) using the procedure of Example 159. ¹H NMR (300 MHz, DMSO-d₆) δ 10.50 (s, 1H), 9.00 (d, 1H), 8.45 (d, 1H), 7.79 (d, 1H), 7.67 (d, 1H), 7.61 (dd, 1H), 7.42 (d, 1H), 7.38 (m, 5H), 4.28 (m, 1H), 4.01 (s, 2H), 2.25 (m, 2H), 2.00 (s, 3H), 1.86 (m, 2H); MS (DCI-NH₃) m/e 470 (M+H)⁺. Anal calcd for C₂₃H₂₃N₃O₄S₂·H₂O: C, 56.66; H, 5.17; N, 8.62. Found: C, 56.75; H, 4.96; N, 8.45.

Example 164[4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester hydrochloride

6680

Example 164A*N*-tert-butoxycarbonyl-(R)-(-)-thiazolidine-4-carboxylic acid

To a solution of (R)-(-)-thiazolidine-4-carboxylic acid (1.0 g, 7.5 mmol) in aqueous 1N NaOH (9 mL) and THF (9 mL) was added a solution of di-*tert*-butyldicarbonate (1.62 g, 7.4 mmol) in THF (9 mL). An additional 2 mL of aqueous NaOH was added and the reaction mixture was stirred overnight at ambient temperature. Additional aqueous NaOH was added to make a clear solution and the reaction mixture was washed with hexanes (3x). The hexane extracts were washed twice with saturated aqueous NaHCO₃. The combined aqueous layers were acidified to pH 2 with 1.1 M NaHSO₄ and extracted twice with ether. The combined ether layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to give *N*-tert-butoxycarbonyl-(R)-(-)-thiazolidine-4-carboxylic acid (1.3 g) which was used without further purification.

6685

6690

Example 164B[4-(*N*-tert-butoxycarbonyl)-(R)-thiazolidin-4-ylcarbonyl]amino-2-phenylbenzoyl]methionine methyl ester

6695

The desired compound was prepared by coupling of *N*-tert-butoxycarbonyl-(R)-(-)-thiazolidine-4-carboxylic acid, prepared as in Example 164A with [4-amino-2-phenylbenzoyl]methionine methyl ester (compound 8) according to the method of Example 163D.

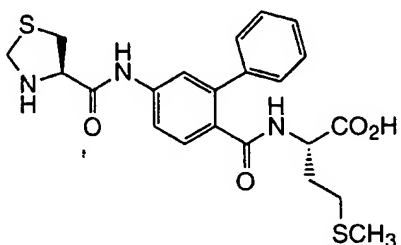
6700

Example 164C[4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester hydrochloride

To a mixture of [4-(*N*-tert-butoxycarbonyl)-(R)-thiazolidin-4-ylcarbonyl]amino-2-phenylbenzoyl]methionine methyl ester (270 mg, 0.47 mmol) and thiophenol (0.1 mL, 0.97 mmol) was added 4N HCl-dioxane (10 mL) and the reaction mixture was stirred for 45

6705

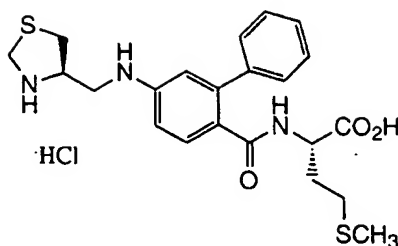
minutes at ambient temperature. The reaction mixture was partitioned between water and ether. The aqueous phase was extracted with ether. The organic extracts were discarded and the aqueous phase was lyophilized to give [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester hydrochloride (150 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 10.53 (s, 1H), 8.45 (d, 1H), 7.68 (m, 2H), 7.42 (dd, 1H), 7.37 (m, 5H), 4.27 (m, 4H), 3.70, 3.25, 3.12 (all m, total 3H), 2.24 (m, 2H), 2.00 (s, 3H), 1.85 (m, 2H); MS (APCI) m/e 474 (M+H)⁺. Anal calcd for C₂₃H₂₈ClN₃O₄S₂·1.4H₂O: C, 51.61; H, 5.80; N, 7.85. Found: C, 51.67; H, 5.55; N, 7.28.



Example 165

[4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine

To a 0 °C solution in methanol (4.3 mL) of [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester hydrochloride (75 mg, 0.15 mmol) was added a solution of lithium hydroxide hydrate (18 mg, 0.43 mmol) in water (0.5 mL). The reaction mixture was stirred for 1.5 hours, then the cold bath was removed and stirring was continued overnight at ambient temperature. The reaction mixture was concentrated in vacuo and aqueous 2N HCl was added to the residue. The cloudy solution was extracted with ethyl acetate and chloroform-isopropanol. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo to give 4-((R)-thiazolidine-4-carbonyl)amino-2-phenylbenzoyl]methionine (67 mg). ¹H NMR (300 MHz, DMSO-d₆) δ 11.10 (s, 1H), 8.60 (d, 1H), 7.70 (s, 1H), 7.68 (dd, 1H), 7.44 (dd, 1H), 7.37 (m, 5H), 4.63 (m, 1H), 4.37 (m, 3H), 3.70 (m, 1H), 3.63 (s, 3H), 3.40 (m, 1H), 2.24 (m, 2H), 2.00 (s, 3H), 1.85 (m, 2H); MS (APCI) m/e 460 (M+H)⁺. Anal calcd for C₂₂H₂₅N₃O₄S₂·0.8 HCl: C, 54.06; H, 5.32; N, 8.60. Found: C, 54.21; H, 5.34; N, 8.00.

Example 166[4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride

6740

Example 166A*N*-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid-*N*-methoxy-*N*-methyl amide

To a solution in DMF (10 mL) of *N*-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid (777 mg, 3.33 mmol), prepared as in Example 164A, 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (602 mg, 3.69 mmol), and ethyl dimethylaminopropyl carbodiimide hydrochloride (709 mg, 3.70 mmol) was added *N*,*O*-dimethylhydroxylamine hydrochloride (357 mg, 3.66 mmol) and 4-methylmorpholine (0.44 mL, 4.01 mmol) and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with ethyl acetate and extracted with aqueous 1M H₃PO₄ (2x), saturated aqueous NaHCO₃ (2x), and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated in vacuo. Chromatography on silica gel (2:1 hexane-ethyl acetate) gave *N*-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid-*N*-methoxy-*N*-methyl amide (605 mg) as a thick yellow oil.

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6750

Example 166B*N*-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxaldehyde

To a -78 °C solution in THF (6 mL) of *N*-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid-*N*-methoxy-*N*-methyl amide (550 mg, 2.0 mmol) was added lithium aluminum hydride (1.0 M in THF, 3.0 mL, 3.0 mmol) and the reaction mixture was stirred for 2.5 hours. The reaction was quenched with 10% aqueous citric acid (30 mL) and warmed to ambient temperature. The mixture was warmed to ambient temperature and extracted with ether (3x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo to give *N*-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxaldehyde (440 mg) which was used without further purification.

6755

6760

Example 166C

6765 [4-(*N*-*tert*-butoxycarbonyl-(R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester

N-*tert*-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxaldehyde was reductively aminated with 4-amino-2-phenylbenzoyl methionine methyl ester (compound 8) according to the procedure of Example 158B.

6770

Example 166C

[4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester

The desired compound was prepared according to the method of Example 164C, except substituting [4-(*N*-*tert*-butoxycarbonyl-(R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 166B, for [4-(*N*-*tert*-butoxycarbonyl-(R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester.

6775

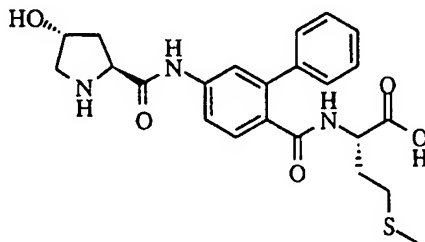
Example 166D

6780 [4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride

The desired compound was prepared by saponification of [4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 166C according to the procedure of Example 165. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.03 (d, 1H), 7.33 (m, 6H), 6.69 (dd, 1H), 6.59 (d, 1H), 4.30 (dd, 2H), 4.23 (m, 1H), 3.86 (m, 1H), 3.46 (dd, 2H), 3.22 (dd, 1H), 2.91 (m, 1H), 2.24 (m, 2H), 2.00 (s, 3H), 1.85 (m, 2H); MS (APCI) *m/e* 446 (M+H)⁺, 444 (M-H)⁻. Anal calcd for C₂₂H₂₇N₃O₃S₂·HCl·0.25H₂O: C, 54.31; H, 5.90; N, 8.64. Found: C, 54.20; H, 6.07; N, 8.35.

6785

6790

Example 169

[4-(4-hydroxy-prolinyl)amino-2-phenylbenzoyl]methionine trifluoroacetate

6795

Example 169A

N-Boc-4-(*t*-butyldimethylsilyl)hydroxyproline

To a solution of 1.3 g (3.6 mmol) of *N*-Boc-4-(*t*-butyldimethylsilyloxy)proline methyl ester, prepared as described by Rosen et al., *J. Med. Chem.* **1988**, *31*, 1598, in 10 ml of methanol was added 5 ml (5 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 30 min. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned between dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 1.05 g (96 %) of *N*-Boc-4-(*t*-butyldimethylsilyl-oxy)proline as a foamy solid which was used without further purification.

Example 169B[4-[*N*-Boc-4-(*t*-butyldimethylsilyloxy)prolinyl]amino-2-phenylbenzoyl]methionine methyl ester

To a solution in dichloromethane (15 mL) of *N*-Boc-4-(*t*-butyldimethylsilyloxy)proline (1.0 g, 3.29 mmol), prepared as in Example 169A, was added 550 μ l (3.9 mmol) of triethylamine in an ice bath under argon, followed by 470 μ l (3.6 mmol) of isobutyl chloroformate. The reaction mixture was stirred for 40 minutes. At this time TLC showed the absence of the starting material. To this solution, 1.07 g (2.97 mmol) of [2-phenyl-4-aminobenzoyl]methionine methyl ester (compound 8) in 10 ml of dichloromethane was introduced. The reaction mixture was stirred overnight, during which time the ice bath expired. The reaction mixture was washed with 1 N HCl, 5 % sodium bicarbonate, and water, dried over magnesium sulfate, and solvent was removed. The residue was flash-chromatographed on silica gel (7:3 hexanes-ethyl acetate) to yield 1.92 g (94 %) of {4-[*N*-Boc-4-(*t*-butyldimethylsilyl)hydroxyprolinyl]-2-phenylaminobenzoyl}methionine methyl ester as a foamy solid. mp 83 °C; $[\alpha]_D^{25}$ -36.2 ($c=0.63$, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.94 (s, 1H), 7.53-7.26 (m, 8H), 6.41 (d, 1H, $J=6.0$ Hz), 4.55 (m, 4H), 3.63 (s, 3H), 3.57 (m, 1H), 3.32 (m, 1H), 2.30 (m, 1H), 2.05 (m, 2H), 1.94 (s, 3H), 1.83 (m, 1H), 1.73 (m, 1H), 1.45 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H); ¹³C NMR (CDCl₃) δ 171.8, 170.7, 169.3, 155.6, 140.0, 129.7, 129.0, 128.5, 128.2, 127.4, 120.2, 117.7, 80.7, 77.2, 70.1, 59.5, 54.7, 52.1, 51.7, 38.0, 30.9, 29.5, 28.2, 25.5, 17.7, 15.1, 4.9; HRMS (EI) calculated for C₃₅H₅₁N₃O₇SSi: 685.9498, found: 685.3217.

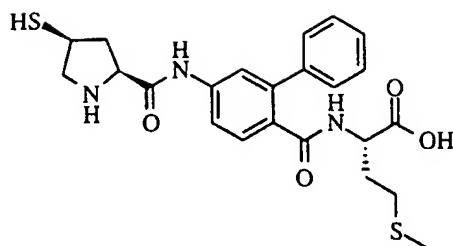
Example 169C[4-(*N*-Boc-4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine methyl ester

To a solution of 1.82 g (2.65 mmol) of {4-[*N*-Boc-4-(*t*-butyldimethylsilyloxy)-prolinyl]amino-2-phenylbenzoyl}methionine methyl ester, prepared as in Example 169B, in 20 ml of THF was added 3 ml (3 mmol) of 1 M tetra-*n*-butylammonium fluoride in THF. The reaction mixture was stirred overnight, diluted with ethyl acetate, and washed 3 times with water. The combined aqueous washings were extracted 3 times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to obtain 864 mg (57 %) of [4-(*N*-Boc-4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine methyl ester as a white solid: mp 121-123 °C; $[\alpha]_D^{25}$ -53.3 ($c=0.43$, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.84 (s, 1H), 7.60-7.38 (m, 8H), 6.35 (br s, 1H), 4.58-4.51 (br s, 4H), 3.64 (s, 3H), 3.57 (m, 1H), 3.48 (m, 1H), 2.63 (m, 1H), 2.44 (br s, 1H), 2.07 (m, 2H), 1.98 (s, 3H), 1.86 (m, 1H), 1.72 (m, 1H), 1.44 (s, 9H); HRMS (EI) calculated for C₂₉H₃₇N₃O₇S: 571.6872, found: 571.2352.

Example 169D

[4-(4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine trifluoroacetate

To a solution of 358 mg (0.62 mmol) of [4-(*N*-Boc-4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 169C, in 6 ml of methanol was added 1 ml (1 mmol) of 1 N LiOH in an ice bath and the reaction mixture was stirred for 4 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned between chloroform and water and extracted 3 times with chloroform. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 317 mg (92 %) of [4-(4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine as a white solid. To a 5 ml of 1:1 solution of TFA and dichloromethane was added 306 mg (0.54 mmol) of the acid. After 3 hours, the reaction mixture was thoroughly evaporated under high vacuum to give an oily residue. The residue was triturated with anhydrous ether and the white solid was collected by filtration to give 254 mg (72%) of [4-(4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine trifluoroacetate: HPLC 90 % (purity); mp 127 (sub.), 154-157 °C (dec.); ¹H NMR (300 MHz, CDCl₃ + CD₃OD) δ 7.53-7.29 (m, 8H), 4.67 (m, 1H), 4.58 (s, 1H), 4.50 (m, 1H), 2.57 (m, 1H), 2.14 (m, 2H), 2.01 (s, 3H), 1.96 (m, 1H), 1.76 (m, 1H); ¹³C NMR (CD₃OD) δ 174.8, 172.6, 168.1, 142.4, 141.2, 140.6, 133.2, 130.0, 129.6, 129.5, 128.8, 122.2, 119.3, 71.2, 60.6, 55.2, 52.9, 39.9, 31.4, 30.9, 15.0.



Example 170

6870

[4-((2S,4S)-4-mercaptopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine trifluoroacetate

Example 170A

6875

[4-((2S,4S)-1-Boc-4-acetylthiopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine methyl ester

6880

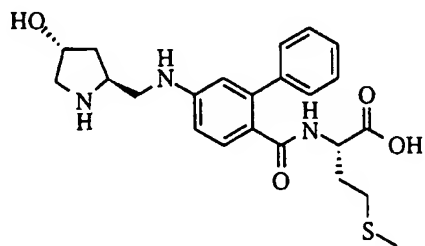
To a solution of 140 mg (0.22 mmol) of {4-[*N*-Boc-4-(*t*-butyldimethylsilyloxy)-prolinyl]amino-2-phenylbenzoyl}methionine methyl ester, prepared as in Example 169C, in 10 ml of THF was added 128 mg (0.48 mmol) of triphenylphosphine, followed by 96 μ l (0.49 mmol) of diisopropyl azodicarboxylate at 0 °C under argon atmosphere. The reaction mixture was stirred for 40 minutes and 35 μ l (0.49 mmol) of thiolacetic acid was added to this mixture at the same temperature. The reaction mixture was stirred overnight, during which time the ice bath expired. The solvent was removed, and a 3:1 solution of hexanes and ethyl acetate was introduced to the resulting residue to precipitate the insoluble by-products. After removal of by-products, the solution was concentrated. The crude product was chromatographed on silica gel (3:1 hexanes-ethyl acetate) to yield 123 mg (89 %) of [4-((2S,4S)-1-Boc-4-acetylthiopyrrolidin-2-carboxy)amino-s-phenylbenzoyl]methionine methyl ester as a foamy solid: mp 97 °C; $[\alpha]_D^{25}$ -105.2 ($c=0.27$, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.87 (s, 1H), 7.68-7.38 (m, 8H), 6.37 (s, 1H), 4.58 (br s, 4H), 4.02 (m, 1H), 3.64 (s, 3H), 3.33 (br s, 1H), 2.52 (br s, 1H), 2.30 (s, 3H), 2.03 (t, 2H, $J=7.8$ Hz), 1.99 (s, 3H), 1.90 (m, 1H), 1.74 (m, 1H), 1.45 (s, 9H); ¹³C NMR (CDCl₃) δ 195.5, 172.2, 169.9, 169.3, 169.0, 155.3, 140.3, 140.0, 130.2, 129.2, 128.7, 128.4, 127.7, 120.6, 117.9, 81.6, 60.2, 53.2, 52.3, 51.9, 39.3, 34.0, 31.2, 30.5, 29.6, 28.3, 15.2; MS (EI) m/z (relative intensity) 629 (M^+ , 6), 571 (25), 529 (45), 196 (100).

6895

Example 170B

[4-((2S,4S)-4-mercaptopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine trifluoroacetate

To a solution of 120 mg (0.19 mmol) of [4-((2S,4S)-1-Boc-4-acetylthiopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 170A, in 5 ml of THF was added 1 ml (1 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 2 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The residue was partitioned between dichloromethane and water and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 105 mg (94 %) of [4-((2S,4S)-4-thiopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine as a white solid. To 5 ml of a 1:1 solution of TFA and dichloromethane were added 105 mg (0.17 mmol) of the acid, followed by a few drops of triethylsilane. After 30 minutes, the reaction mixture was thoroughly evaporated in high vacuum to give an oily residue. The residue was triturated with anhydrous ether and the white solid was collected by filtration to give 90 mg (80%) of [4-((2S,4S)-4-thiopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine trifluoroacetate: HPLC 86 % (purity); mp 169 °C (dec.); ¹H NMR (300 MHz, CD₃OD) δ 7.59-7.28 (m, 8H), 4.39 (m, 2H), 3.53 (m, 1H), 3.38 (m, 1H), 3.22-3.12 (m, 2H), 2.87 (m, 1H), 2.12 (m, 1H), 2.00-1.92 (m, 5H), 1.72 (m, 1H); ¹³C NMR (CD₃OD) δ 175.0, 172.7, 167.5, 142.6, 140.7, 133.4, 130.2, 129.8, 129.7, 129.0, 122.5, 119.5, 61.8, 55.3, 53.2, 41.1, 36.2, 31.6, 31.1, 15.3.



6920

Example 171

[4-((2S,4R)-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride

Example 171A

6925

(2S,4R)-1-Boc-4-[(*t*-butyldimethylsilyloxy]-2-(hydroxymethyl)pyrrolidine

6930

A suspension of calcium chloride (780 mg, 7 mmol) and 530 mg (14 mmol) of sodium borohydride in 25 ml of THF was stirred at ambient temperature for 5 hours. To this suspension was added 2.5 g (7 mmol) of (2S,4R)-1-Boc-4-[(*t*-butyldimethylsilyloxy]-2-(carbomethoxy)pyrrolidine methyl ester in 5 ml of THF and the reaction mixture was stirred overnight. Excess hydride was destroyed by adding hydrated sodium sulfate. The white

precipitate was removed by suction filtration through a pad of Celite, and the filtrate was dried over magnesium sulfate and concentrated to give 2.25 g (97 %) of (2S,4R)-1-Boc-4-[(*t*-butyldimethylsilyloxy)-2-(hydroxymethyl)pyrrolidine as a colorless oil: ¹H NMR (CDCl₃) δ 0.05 (s, 6H), 0.85 (s, 9H), 1.47 (s, 9H), 1.90 (m, 1H), 3.27-4.25 (complex m, 7H), 4.89 (br d, 1H, *J*=6.6 Hz): MS (EI) *m/z* 332 (M⁺), 258.

Example 171B

(2S,4R)-1-Boc-4-[(*t*-butyldimethylsilyloxy)pyrrolidin-2-aldehyde

To a solution of 1 ml (14.1 mmol) of DMSO in 7 ml of dichloromethane were added 1.48 ml (10.4 mmol) of trifluoroacetic anhydride in 3.5 ml of dichloromethane at -78 °C under a slight stream of argon. After 10 min, 2.35 g (7 mmol) of (2S,4R)-1-Boc-4-[(*t*-butyldimethylsilyloxy)-2-(hydroxymethyl)pyrrolidine, prepared as in Example 171A, in 7 ml of dichloromethane was added to this mixture at the same temperature. The reaction mixture was stirred for 1 hour. To this solution was added 3 ml (21.5 mmol) of triethylamine. The reaction mixture was stirred for 1 hour at -78 °C, slowly warmed to room temperature, and concentrated. The residue was chromatographed on silica gel (9:1 hexanes-ethyl acetate to yield 1.08 g (47 %) of (2S,4R)-1-Boc-4-[(*t*-butyldimethylsilyloxy)-pyrrolidin-2-aldehyde as an oil: ¹H NMR (300 MHz, CDCl₃) δ 9.39 (s, 1H), 4.33 (m, 1H), 4.17 (m, 1H), 3.48 (m, 1H), 3.35 (m, 1H), 1.93 (m, 2H), 1.41 (s, 9H), 0.82 (s, 9H), 0.07 (s, 6H).

Example 171C

{4-[(2S,4R)-1-Boc-4-*t*-butyldimethylsilyloxy]pyrrolidin-2-ylmethyl}amino-2-phenylbenzoyl}methionine methyl ester

To a solution of 0.75 g (2.09 mmol) of [2-phenyl-4-aminobenzoyl]methionine methyl ester (compound 8) and 0.7 g (2.1 mmol) of (2S,4R)-1-Boc-4-[(*t*-butyldimethylsilyloxy)-pyrrolidin-2-aldehyde, prepared as in Example 171B, in 10 ml of methanol were added 1 ml of acetic acid, followed by 0.2 g (3.1 mmol) of sodium cyanoborohydride. The reaction mixture was stirred overnight. After removal of the solvent, the residue was partitioned with ethyl acetate and 5 % sodium bicarbonate, and extracted 3 times with ethyl acetate. The combined organic solution was washed with water and brine, dried over magnesium sulfate, and solvent was removed. The residue was flash-chromatographed on silica gel (2:1 hexanes-ethyl acetate) to yield 261 mg (74 %) of {4-[(2S,4R)-1-Boc-4-[(*t*-butyldimethylsilyloxy)pyrrolidin-2-ylmethyl]amino-2-phenylbenzoyl}methionine methyl ester as a white solid: mp 48 °C; [α]_D²⁵ -15.6 (*c*=1.03, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.67 (d, 1H, *J*=8.5 Hz), 7.37 (m, 6H), 6.57 (1, 1H), 6.37 (s, 1H), 5.60 (br s, 2H), 4.60 (m, 1H), 4.31 (m, 2H), 3.77 (s, 3H), 3.61-3.10 (m, 5H), 2.06 (t, 2H, *J*=8.2 Hz), 1.98 (s, 3H), 1.85 (m, 1H), 1.60 (m, 1H), 1.43 (s, 9H);

0.84 (s, 9H), 0.03 (s, 6H); HRMS (EI) calculated for C₃₅H₅₃N₃O₆SSi: 671.3424, found: 671.3424.

6970

Example 171D

[4-((2S,4R)-N-Boc-4-hydroxy)pyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester

To a solution of 770 mg (1.14 mmol) of {4-[(2S,4R)-1-Boc-4-(*t*-butyldimethylsilyloxy)-pyrrolidin-2-ylmethyl]amino-2-phenylbenzoyl}methionine methyl ester, prepared as in Example 171C, in 10 ml of THF was added 2 ml (2 mmol) of 1 M tetra-*n*-butylammonium fluoride in THF. The reaction mixture was stirred for 15 minutes at ambient temperature, diluted with ethyl acetate, and washed 3 times with water. The combined aqueous washings were extracted 3 times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to obtain 467 mg (73 %) of 2-[4-((2S,4R)-N-Boc-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester as a foamy solid: mp 81 °C; [α]_D²⁴ -15.9 (*c*=0.74, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.63 (d, 1H, *J*=9.0 Hz), 7.35 (m, 6H), 6.57 (br s, 1H), 6.38 (br s, 1H), 5.67 (d, 1H, *J*=7.6 Hz), 5.54 (br s, 1H), 4.55 (m, 1H), 4.09 (m, 2H), 3.59 (s, 3H), 3.37-3.16 (m, 5H), 2.71 (br s, 1H), 2.04 (m, 2H), 1.96 (s, 3H), 1.80 (m, 1H), 1.60 (m, 1H), 1.40 (s, 9H); ¹³C NMR (CDCl₃) δ 172.0, 168.5, 156.4, 150.0, 141.7, 141.1, 131.3, 128.6, 127.7, 121.8, 113.5, 110.8, 80.2, 69.5, 69.1, 60.3, 55.3, 54.8, 52.2, 51.7, 49.0, 38.6, 31.5, 29.4, 28.3, 25.5, 15.2; HRMS (EI) calculated for C₂₉H₃₉N₃O₆S: 557.2559, found: 557.2559.

6990

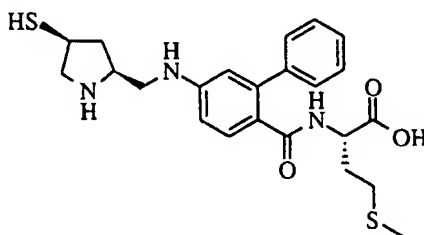
Example 171E

[4-((2S,4R)-N-Boc-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride

To a solution of 125mg (0.22 mmol) of [4-((2S,4R)-N-Boc-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 171D, in 5 ml of THF was added 0.5 ml (0.5 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 5 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The residue was partitioned with dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 50 mg (42 %) of the resulting free acid as a solid. To a 2 ml of 1:1 solution of TFA and dichloromethane was added 50 mg (0.09 mmol) of the acid. After 30 minutes, the reaction mixture was thoroughly evaporated in high vacuum to

7000

7005 give an oily residue. The residue was triturated with 0.3 ml of 3 M anhydrous HCl-ether in
 5 ml of ether and the white solid was collected by filtration to give 35 mg (74 %) of [4-
 ((2S,4R)-N-Boc-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine
 hydrochloride: HPLC 72 % (purity). ¹H NMR (300 MHz, CD₃OD) δ 7.71-7.30 (m, 6H),
 6.76 (dd, 1H, *J* = 8.4, 2.4 Hz), 6.69 (d, 1H, *J* = 2.2 Hz), 4.55 (d, 1H, *J* = 4.0 Hz), 4.44
 7010 (dd, 1H, *J* = 9.3, 4.2 Hz), 4.12 (m, 1H), 3.62-3.19 (m, 4H), 2.02 (s, 3H), 2.21-1.75 (m,
 6H).



7015

Example 172

[4-((2S,4S)-4-thiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine hydrochloride

Example 172A

[4-((2S,4S)-N-Boc-4-acetylthiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine

7020

methyl ester and

[4-((2S,5S)-4-Boc-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenyl]benzoyl]methionine methyl
ester

To a solution of 153 mg (0.27 mmol) of 2-Phenyl-4-[(2S,4R)-N-Boc-4-
 hydroxy]pyrrolidine-2-methyl]aminobenzoylmethionine methyl ester, prepared as in
 7025 Example 171D, in 10 ml of THF were added 142 mg (0.54 mmol) of triphenylphosphine,
 followed by 107 μ l (0.54 mmol) of diisopropyl azodicarboxylate at 0 °C under argon
 atmosphere. The mixture was stirred for 30 minutes and 40 μ l (0.56 mmol) of thiolacetic
 acid was added at the same temperature. The reaction mixture was stirred overnight, during
 which time the ice bath expired. The solvent was removed, and a 3:1 solution of hexanes
 7030 and ethyl acetate was introduced to the residue to precipitate the insoluble by-products. After
 removal of by-products, the solution was concentrated. The crude products were
 chromatographed on silica gel (1:1 hexanes-ethyl acetate) to give 106 mg (63 %) of [4-
 ((2S,4S)-N-Boc-4-acetylthiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine
 methyl ester and 35 mg (24 %) of the bicyclic [4-((2S,5S)-4-Boc-1,4-
 7035 diazabicyclo(2,2,1)octan-1-yl)-2-phenyl]benzoyl]methionine methyl ester as white solids.

[4-((2S,4S)-N-Boc-4-acetylthiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine methyl ester: ¹H NMR (300 MHz, CDCl₃) δ 7.65 (d, 1H, J=8.4 Hz), 7.37 (m, 6H), 6.60 (br s, 1H), 6.41 (br s, 1H), 5.66 (d, 1H, J=7.8 Hz), 5.53 (br s, 1H), 4.58 (m, 1H), 4.23 (br s, 1H), 4.02 (br s, 1H), 3.87 (m, 1H), 3.60 (s, 3H), 3.38-3.12 (br s, 2H), 3.12 (dd, 1H, J=6.7, 11.4 Hz), 2.52 (m, 1H), 2.30 (s, 3H), 2.05 (t, 2H, J=7.6 Hz), 1.97 (s, 3H), 1.82 (m, 1H), 1.62 (m, 1H), 1.41 (s, 9H); ¹³C NMR (CDCl₃) δ 195.0, 172.1, 168.5, 155.8, 150.0, 141.8, 141.4, 131.5, 128.8, 128.6, 127.8, 122.2, 113.7, 111.0, 80.7, 60.4, 56.5, 52.3, 51.8, 49.2, 39.3, 36.0, 31.7, 30.6, 29.6, 28.4, 15.3; HRMS (EI) calculated for C₃₁H₄₁N₃O₆S₂: 615.2436, found: 615.2436.

[4-((2S,5S)-4-Boc-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine methyl ester: ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, 1H, J=8.6 Hz), 7.54-7.40 (m, 6H), 6.57 (d, 1H, J=9.0 Hz), 6.36 (s, 1H), 5.68 (br s, 1H), 4.63 (m, 2H), 4.42 (br s, 1H), 3.63 (s, 3H), 3.58-3.17 (m, 5H), 2.10 (m, 2H), 1.98 (s, 3H), 1.86 (m, 1H), 1.66 (m, 1H), 1.41 (s, 9H); ¹³C NMR (CDCl₃) δ 172.2, 168.5, 154.2, 148.7, 142.0, 141.4, 132.1, 131.7, 129.0, 128.8, 128.1, 122.1, 113.7, 111.2, 80.0, 57.4, 56.4, 52.5, 52.0, 37.9, 37.4, 31.9, 29.7, 28.7, 15.5; HRMS (EI) calculated for C₂₉H₃₇N₃O₅S: 539.2454, found: 539.2453.

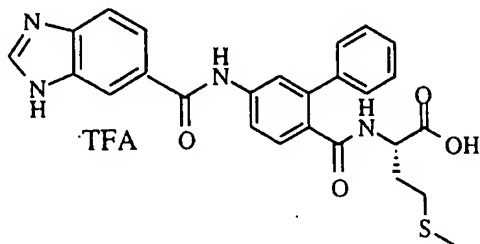
Example 172B

[4-((2S,4S)-4-thiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine hydrochloride

To a solution of 86 mg (0.14 mmol) of [4-((2S,4S)-N-Boc-4-acetylthiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine methyl ester in 2 ml of THF was added 0.4 ml (0.4 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 2 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned between dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 67 mg (85 %) of the resulting free acid as a white solid. To 2 ml of 1:1 solution of TFA and dichloromethane were added 67 mg (0.12 mmol) of the acid, followed by a few drops of triethylsilane. After 30 minutes, The reaction mixture was thoroughly evaporated under high vacuum to give an oily residue. The residue was triturated with anhydrous ether and the white solid was collected by filtration to give 62 mg (97 %) of [4-((2S,4S)-4-thiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine hydrochloride: HPLC 83% (purity); ¹H NMR (300 MHz, CD₃OD) δ 7.46-7.35 (m, 6H), 6.76 (d, 1H, J=8.4 Hz), 6.70 (s, 1H), 4.45 (m, 1H), 3.91 (m, 1H), 3.68-3.30 (m, 5H), 3.15 (m, 1H), 2.66 (m, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 2.01 (s, 3H), 1.79 (m, 2H); ¹³C NMR

(CD₃OD) δ 175.0, 173.3, 150.5, 143.5, 142.3, 131.3, 129.9, 129.6, 128.7, 125.9, 115.9, 112.5, 60.9, 54.6, 53.3, 45.8, 40.3, 35.4, 31.8, 31.0, 15.3.

7075



Example 182

[4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine trifluoroacetate

7080

Example 182A

(1H-1-*p*-Toluenesulfonylbenzimidazol-5-yl)carboxylic acid

5-Benzimidazolecarboxylic acid (1.0 g, 6.2 mmol) and *p*-toluenesulfonyl chloride (1.2 g, 6.2 mmol) were suspended in 10 mL of distilled water. Aqueous 1N sodium hydroxide was added periodically to maintain a pH of approximately 9 over a period of 4 hours. The reaction mixture was washed with methylene chloride (3X50 mL.) and was adjusted to pH 3 with 1N hydrochloric acid. The precipitate which formed was collected by vacuum filtration, washed with distilled water and hexanes and air dried to give (1H-1-*p*-toluenesulfonylbenzimidazol-5-yl)carboxylic acid (0.75 g, 38%) as a white solid.

7090

Example 182B

[4-(1H-1-*p*-Toluenesulfonylbenzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester

To 50 mL of methylene chloride containing [4-amino-2-phenylbenzoyl]methionine methyl ester hydrochloride (compound 8, 0.65 g, 1.64 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 0.34 g, 1.8 mmol) was added (1H-1-*p*-toluenesulfonylbenzimidazol-5-yl)carboxylic acid (0.52 g, 1.64 mmol), prepared as in Example 182A, and the mixture was cooled to 0°C. Triethylamine (0.16 g, 1.64 mmol) was slowly added to the stirred solution. After 1 hour, the ice bath was removed and the reaction was stirred for an additional 96 hours. The organic layer was washed with distilled water, dried over magnesium sulfate and concentrated. The residue was purified by flash column chromatography (4:1 ethyl acetate/hexanes) to give [4-(1H-1-*p*-toluenesulfonylbenzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester (0.63 g, 59%) as a white solid.

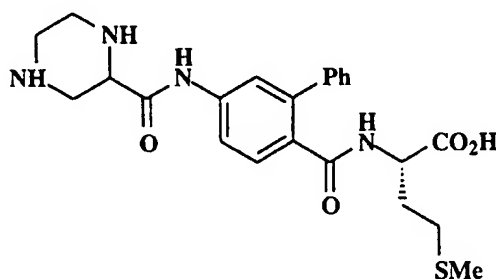
Example 182C

7105

[4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine trifluoroacetate

7110 [4-(1H-1-*p*-Toluenesulfonylbenzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester (0.2 g, 0.3 mmol), prepared as in Example 182B, was added to 5 mL of tetrahydrofuran (THF) and the mixture was cooled to 0°C. Lithium hydroxide (5 mL, 0.5M) was slowly added and the reaction mixture was stirred for 2 hours. The THF was removed by evaporation and 0.5M HCl was added to adjust the pH to between 2 and 3 and the precipitate which formed was collected by vacuum filtration. The solid was purified by reverse phase preparative HPLC (Waters 25X10 cm, C-18 column, 220 nm UV detector, flow rate 15 mL/min, linear gradient from 5% acetonitrile and 95% water containing 0.1% TFA to 60% acetonitrile in 40 minutes) and pure fractions were pooled and lyophilized to give [4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine trifluoroacetate as a white solid (0.146 g, 87%). ¹H NMR (300 MHz, DMSO-d₆) δ 10.56 (s, 1H), 9.05 (s, 1H), 8.47 (d, 1H, *J* = 7.8 Hz), 8.40 (s, 1H), 8.04 (d, 1H, *J* = 8.1 Hz), 7.88-7.89 (m, 2H), 7.33-7.48 (m, 6H), 4.30 (m, 1H), 2.16-2.29 (m, 2H), 2.06 (s, 3H), 1.84-2.00 (m, 2H). MS *m/e* 489 (M+H)⁺.

7120

Example 185

7125

[4-(piperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine hydrochloride.Example 185Adi-*tert*-butoxycarbonylpiperidine-2-carboxylic acid

7130 Di-*tert*-butyl dicarbonate (15.5 g, 70.2 mmol) was added to a solution of piperazine-2-carboxylic acid (4.85 g, 23.4 mmol) and NaOH (98 mL of a 1 M aqueous solution, 98 mmol) in THF (100 mL). The cloudy mixture was stirred for 16 hours and then concentrated under reduced pressure to remove THF. The residue was saturated with solid NaHCO₃ and extracted with ether (2 x 30 mL). The aqueous layer was cooled to 0 °C and then adjusted to pH = 3 with 2 M aqueous HCl. A precipitate developed. The mixture was

7135 extracted with CH₂Cl₂ (3 x 75 mL), and the organic extracts were dried over MgSO₄,
filtered, and concentrated under reduced pressure to provide 7.61 g (98%) of di-*tert*-
butoxycarbonylpiperidine-2-carboxylic acid as a tan solid. ¹H NMR (CDCl₃) δ 1.45 (s, 18
H), 2.80-2.98 (br, 1 H), 3.04-3.36 (br comp, 2 H), 3.70-3.83 (br, 1 H), 3.94-4.05 (br, 1
H), 4.44-4.65 (br comp, 2 H), 4.80-4.95 (br, 1 H). LRMS (CI): 292, 331 (M+1)⁺, 348
7140 (M+NH₄)⁺.

Example 185B

[4-(di-*tert*-butoxycarbonylpiperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl
ester.

7145 The desired compound was prepared by coupling di-*tert*-butoxycarbonylpiperidine-2-
carboxylic acid with [4-amino-2-phenylbenzoyl]methionine methyl ester (compound 8)
according to the procedure of Example 184A.

Example 185C

7150 [4-(di-*tert*-butoxycarbonylpiperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine.

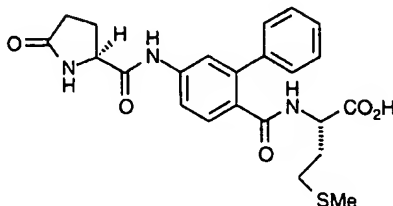
Lithium hydroxide hydrate (0.411 g, 9.60 mmol) was added to a solution of [4-(di-*tert*-
butoxycarbonylpiperidin-2-yl)carboxyamino-2-phenylmethionine methyl ester (*ca* 0.8 g,
1.20 mmol), prepared in Example 185B, in THF/H₂O (4:1, 12 mL). The solution was
stirred for 20 hours and then treated with 1 M aqueous HCl (10 mL). The mixture was
7155 extracted with ethyl acetate (5 x 10 mL), and the organic extracts were rinsed with 1:1 brine/1
N HCl (10 mL), dried over Na₂SO₄, and concentrated under reduced pressure to provide [4-
(di-*tert*-butoxycarbonylpiperidin-2-yl)carboxyamino-2-phenylmethionine (0.72 g) as a white
foam (est. 89%). ¹H NMR (CD₃OD) δ 1.3-1.5 (br, 18 H), 1.7-1.9 (br comp, 2 H), 2.0
(br s, 3 H), 2.1-2.3 (br comp, 2 H), 2.9-4.8 (br comp, 8 H), 7.3-7.5 (br comp, 6 H), 7.5-
7160 7.6 (br m, 1 H), 7.6-7.7 (br m, 1 H). LRMS (CI): 657 (M+1)⁺, 457, 330.

Example 185D

[4-(piperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine hydrochloride.

[4-(di-*tert*-butoxycarbonylpiperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine
7165 (0.72 g, 1.07 mmol), prepared in Example 185C, was treated with HCl (9.6 mL of a 4 M
solution in dioxane, 38.5 mmol) and the solution was stirred for 5 minutes, at which time a
pink precipitate was observed. The mixture was treated with pentane (10 mL) and the
precipitate was isolated by filtration to afford [4-(piperidin-2-yl)carboxyamino-2-
phenylbenzoyl]methionine hydrochloride (0.448 g, 86%). ¹H NMR (CD₃OD) δ 1.73-1.88
7170 (m, 1 H), 1.93-2.05 (comp, 4 H), 2.05-2.14 (m, 1 H), 2.14-2.26 (m, 1 H), 3.32-3.64

(comp, 5 H), 3.68-3.85 (comp, 2 H), 3.97 (dd, 1 H), 4.13 (dd, 1 H), 4.73 (dd, 1 H), 7.35-7.50 (comp, 5 H), 7.51-7.59 (m, 1 H), 7.74-7.80 (m, 1 H). LRMS (CI): 457 (M+1)⁺.



Example 202

[4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine

Example 202A

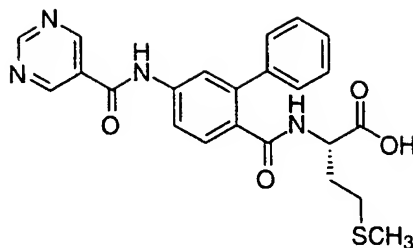
[4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester

To a solution of L-pyrogutamic acid (49mg, 0.38 mmol) in 5 mL of DMF was added 3-hydroxy 1,2,3-benzotriazin-4(3H)-one (62mg, 0.38 mmol), (3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (58mg, 0.30 mmol) and [4-amino-2-phenylbenzoyl-L-methionine methyl ester (90mg, 0.38 mmol), prepared as in Example 192B, and the reaction mixture was stirred at 25 °C for 12 hours. The reaction mixture was taken up in ethyl acetate and washed with 10 mL 1N HCl, 5 mL satd aqueous NaHCO₃ and brine (3 x 10 mL). The organic layer was dried over Na₂SO₄, filtered and evaporated. Purification by radial chromatography (2-5% methanol-ethyl acetate gradient) to give [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester (92mg, 79%) as a white solid.

Example 202B

[4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine

LiOH monohydrate (29mg, 0.69 mmol) was dissolved in 1 mL H₂O and added to a solution of [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 202A, (108mg, 0.23 mmol) in 3 mL of THF and the reaction mixture was stirred at 25 °C for 1 hour. The reaction mixture was evaporated and 2 mL of 1N HCl was added to the aqueous residue. The resulting precipitate was filtered and dried under vacuum to give [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine (96 mg, 91%). ¹H NMR (300 MHz, CD₃OD) δ 7.70 - 7.60 (m, 3H), 7.45 - 7.30 (m, 5H), 4.40 (bs, 1H), 2.60 - 2.10 (m, 7H), 2.00 (s, 3H), 1.90 - 1.80 (m, 2H). CIMS MH⁺ 456.

Example 219[4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine

7205

Example 219A5-pyrimidinecarboxylic acid methyl ester

A mixture of 5-bromopyrimidine (1.59 g, 10 mmol), 1-propanol (1.5 mL, 20 mmol), bis(triphenylphosphine)palladium(II) chloride (400 mg, 0.50 mmol) and tributylamine (3.72 g, 20 mmol) in DMF was stirred at 90 °C under a carbon monoxide balloon for 10 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with potassium dihydrogenphosphate (1.0 M, 20 mL, twice), water, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography (50:50:10 hexane-dichloromethane-ether) to give 3-pyrimidinecarboxylic acid methyl ester (715 mg, 52%). ¹H NMR (300 MHz, CDCl₃) δ 9.38 (s, 1H), 9.30 (s, 2H), 4.36 (t, 2H), 1.83 (sextet, 2H), 1.05 (t, 3H).

7210

7215

Example 219B[4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester

A mixture of the 5-pyrimidinecarboxylic acid methyl ester prepared in Example 219A (682 mg, 4.94 mmol) and aqueous sodium hydroxide solution (4.0 M, 2.5 mL) in THF was heated at 60 °C for 1.5 hours. Hydrochloric acid (6.0 N, 2 mL) was added to the reaction mixture, and the solvent was evaporated *in vacuo*. The residue was dried under high vacuum at 50 °C for 1 hour, and the redissolved in THF. To the acid solution was added (4-amino-2-phenylbenzoyl)methionine methyl ester (compound 8, 1.97 g, 5.0 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (0.978 g, 6.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.15 g, 6.0 mmol) and triethylamine (2.8 mL, 20 mmol). After 14 hours, the reaction mixture was diluted with ethyl acetate (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography (50% ethyl acetate-hexane, then ethyl acetate) to give [4-(3-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester (0.937 g, 41%). ¹H NMR (300 MHz, CDCl₃) δ 9.34 (s, 1H), 9.19 (s, 2H), 9.01 (s, 1H), 7.64 (d, 1H), 7.52 (d, 1H), 7.42 (dd, 1H), 7.33 (m, 5H), 6.20 (br d, 1H), 4.66 (m, 1H),

7225

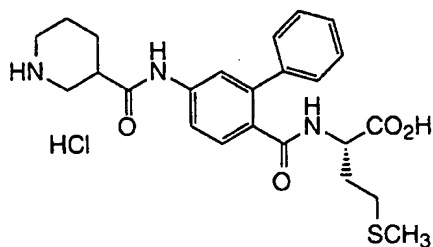
7230

3.69 (s, 3H), 2.14 (t, 2H), 2.02 (s, 3H), 1.95 (m, 1H), 1.78 (m, 1H). MS (CI⁺) m/e 465 (M+H)⁺.

Example 219C

[4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine

To a solution of the [4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester prepared in Example 210B (324 mg, 0.70 mmol) in methanol (2 mL) was added aqueous sodium hydroxide (2.0 N, 1.0 mL). After 14 hours, the reaction mixture was diluted with ethyl acetate (100 mL), washed twice with potassium dihydrogenphosphate (1.0 M, 20 mL each), water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography (ethyl acetate, then 95:5:0.5 ethyl acetate-methanol-acetic acid) to give [4-(3-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine (265 mg, 84%). ¹H NMR (300 MHz, DMSO-d₆) δ 10.80 (s, 1H), 9.38 (s, 1H), 9.30 (s, 2H), 8.51 (d, 1H), 7.83 (m, 2H), 7.50 (d, 1H), 7.39 (m, 5H), 4.29 (m, 1H), 2.28 (m, 2H), 2.00 (s, 3H), 1.86 (m, 2H). MS (APCI⁺) m/e 451 (M+H)⁺.



Example 231

[4-(3-piperidinecarboxyamino)-2-phenylbenzoyl]methionine hydrochloride

7255

Example 231A

1-tert-butoxycarbonylpiperidine-3-carboxylic acid

To a mixture of piperidine-3-carboxylic acid (1.29 g, 10 mmol) in THF (20 mL) was added aqueous 4N sodium hydroxide (5 mL) and di-tert-butylidicarbonate (2.62 g, 12 mmol) and the reaction mixture was stirred for 6 hours. The reaction mixture was acidified with 3N HCl (7 mL) and extracted three times with ethyl acetate. The combined organic extracts were washed with water (2x) and brine, dried, filtered, and concentrated *in vacuo* to give 1-tert-butoxycarbonylpiperidine-3-carboxylic acid (2.11 g) as a white solid.

7265

Example 231B

[4-(1-*tert*-butoxycarbonylpiperidin-3-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester

The desired compound was prepared by coupling of the product of Example 231A and (4-amino-2-phenylbenzoyl)methionine methyl ester (compound 8) according to the method of Example 186C.

Example 231C

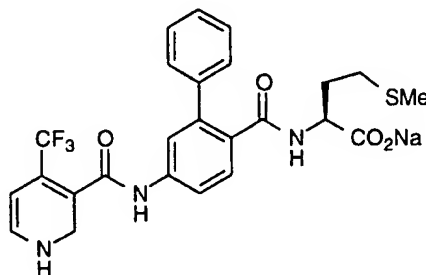
[4-(1-*tert*-butoxycarbonylpiperidin-3-ylcarboxyamino)-2-phenylbenzoyl]methionine

The desired compound was prepared by saponification of the product of Example 231B according to the procedure of Example 159.

Example 231D

[4-(3-piperidinecarboxyamino)-2-phenylbenzoyl]methionine hydrochloride

The product of Example 231C was deprotected with 4N HCl-dioxane using the procedure of Example 229B. ¹H nmr (300 MHz, D₂O) δ 7.37 - 7.60 (m, 8H), 4.44 (dd, 1H), 3.46 (dd, 1H), 3.31 (m, 2H), 1.14 (m, 1H), 3.02 (m, 1H), 1.71 - 2.11 (m, 8H), 2.02 (s, 3H). MS (CI NH₃) M/e 456 (M+H⁺, 438, 408, 339, 307, 196. Anal calcd for C₂₄H₃₀ClN₃O₄S•2.54 H₂O: C, 53.60; H, 6.57; N, 7.59. Found: C, 53.60; H, 6.19; N 7.59.



Example 283

[4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoyl]methionine sodium salt

Example 283A

(4-nitro-2-phenylbenzoyl)methionine 2-trimethylsilylethyl ester

A mixture of (4-nitro-2-phenylbenzoyl)methionine methyl ester (7.69 g, 30 mmol), prepared as in Example 192A and aqueous saturated lithium hydroxide (20 mL) in methanol (50 mL) was refluxed for 6 hours. The reaction mixture was carefully acidified with

concentrated hydrochloric acid (10 mL), and extracted with ethyl acetate (4x). The combine extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in dichloromethane (50 mL) and THF (10 mL) and 2-trimethylsilylethanol (3.72 g, 31.5 mmol), 1,3-diisopropylcarbodiimide (5.17 mL, 33 mmol) and 4-dimethylaminopyridine (30 mg) were added sequentially. After 4 hours, aqueous hydrochloric acid (0.1 N, 0.5 mL) was added and the reaction mixture was stirred for another 2 hours. The reaction mixture was then filtered through silica gel (40 g), and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (5% ethyl ether-hexane) to give the title compound (8.90 g, 87%).

Example 283B

(4-amino-2-phenylbenzoyl)methionine 2-trimethylsilylethyl ester

A mixture of the product of Example 283A (8.85 g, 25.8 mmol), ammonium formate (4.88 g, 77.4 mmol) and palladium (10%) on carbon (1 g) in methanol was refluxed for 5 hours. The mixture was then filtered through Celite and rinsed with ethyl acetate. The filtrate was diluted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound which was used without further purification.

Example 283C

4-(4-trifluoromethylpyrid-3-ylcarbonylamino)-2-phenylbenzoic acid 2-trimethylsilylethyl ester

A mixture of 4-trifluoromethylnicotinic acid (472 mg, 2.46 mmol), the product of Example 283B (771 mg, 2.46 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (481 mg, 2.95 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (566 mg, 2.95 mmol) in DMF (8 mL) was stirred room temperature for 15 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% ethyl acetate-hexane) to give the title compound (1.04 g, 87%).

Example 283D

4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoic acid 2-trimethylsilylethyl ester

A solution of the product of Example 283C (1.02 g, 2.09 mmol), tetrabutylammonium borohydride (539 mg, 2.1 mmol) in 1,2-dichloroethane (10 mL) was heated at 80 °C for 6 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate, water and brine, dried over anhydrous magnesium

sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% ethyl acetate-hexane) to give the title compound (247 mg, 24%).

Example 283E

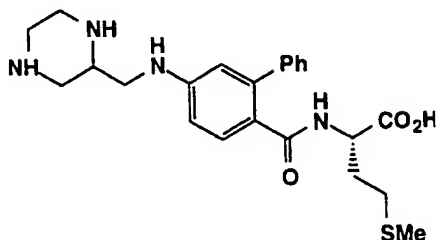
[4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester

A solution of the product of Example 283D (227 mg, 0.48 mmol) and tetrabutylammonium fluoride (261 mg, 1.0 mmol) in dioxane was heated at 80 °C for 90 min. The solvent was then evaporated, and the residue was further dried under high vacuum (2 mmHg) for 1 hour. To the residue was added *L*-methionine methyl ester hydrochloride (115 mg, 0.58 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (163 mg, 1.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (192 mg, 1.0 mmol), DMF (5 mL) and triethylamine (0.3 mL). After 15 hours, the reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (50% ethyl acetate-hexanes) to give the title compound (179 mg, 69%).

Example 283F

[4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoyl]methionine sodium salt

The desired compound was prepared by saponification of the product of Example 283E using the procedure of Example 276. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.67 (s, 1H), 8.87 (br s, 1H), 7.68 (m, 2H), 7.54 (s, 1H), 7.41-7.30 (m, 6H), 7.03 (dd, 1H), 6.51 (d, 1H), 4.67 (t, 1H), 4.48 (m, 1H), 3.78 (m, 1H), 2.14 (m, 2H), 1.96 (s, 3H), 1.77 (m, 2H). MS (APCI⁺) *m/e* 520 (M+H)⁺.



Example 286

[4-(2-piperazinylmethylamino)-2-phenylbenzoyl]methionine

Example 286A

di-tert-butyloxycarbonylpiperidine-2-carboxylic acid

Di-tert-butyl dicarbonate (15.5 g, 70.2 mmol) was added to a solution of piperazine-2-carboxylic acid (4.85 g, 23.4 mmol) and NaOH (98 mL of a 1 M aqueous solution, 98 mmol) in THF (100 mL). The cloudy mixture was stirred for 16 hours and then was concentrated under reduced pressure to remove THF. The aqueous solution was saturated with NaHCO₃ (s) and then extracted with ether (2x). The aqueous layer was cooled to 0 °C and then adjusted to pH 3 with 2 M aqueous HCl during which time a precipitate formed. The mixture was extracted with CH₂Cl₂ (3x), and the organic extracts were dried (MgSO₄) and concentrated under reduced pressure to provide the desired compound (7.61 g, 98% as a tan solid.

Example 286B

di-tert-butyloxycarbonylpiperidine-2-carboxylic acid N-methyl N-methoxy amide

Triethylamine (1.75 g, 17.1 mmol) was added dropwise to a solution of N,O-dimethylhydroxylamine hydrochloride (0.741 g, 7.44 mmol), the product of Example 286A (2.46 g, 7.44 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.61 g, 9.67 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.89 g, 9.67 mmol) in DMF (75 mL). The reaction mixture was stirred at ambient temperature for 20 hours and then concentrated under reduced pressure (50 °C, 0.1 mm Hg). The residue was dissolved in ethyl acetate (70 mL), and the solution was extracted with saturated aqueous NaHCO₃ (3x) and brine. The organic phase was dried (MgSO₄) and concentrated to provide a golden wax. Flash column chromatography (20% ethyl acetate-hexane) afforded the desired compound (2.29 g) which was shown to be 78% pure by ¹H NMR.

Example 286C

di-tert-butyloxycarbonylpiperidine-2-carboxaldehyde

A solution of the product of Example 286B (0.971 g, 2.81 mmol) in THF (4 mL) was added dropwise to a slurry of LAH (0.112 g, 2.81 mmol) in THF (4 mL) at -50 °C. After 10 minutes the bath temperature was adjusted to -10 °C for 10 min and then returned to -50 °C. The addition of saturated aqueous KHSO₄ (8 mL) produced vigorous gas evolution, after which reaction mixture was allowed to warm to ambient temperature over 20 minutes and then filtered through Celite. The filtrate was extracted with 1 N HCl (2x), saturated aqueous NaHCO₃ (2x) and finally brine. The organic phase was dried (MgSO₄) and concentrated to provide the desired compound (0.304 g, 41%) as an amber oil.

Example 286D

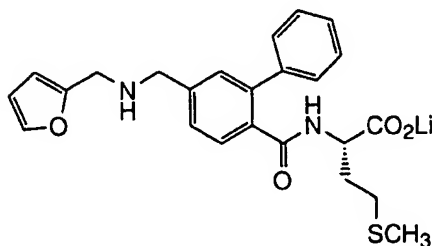
[4-(*di-tert*-butoxycarbonylpiperazin-2-ylmethylamino)-2-phenylbenzoyl]methionine methyl ester

The aldehyde prepared in Example 286C (0.599 g, 1.71 mmol) was added to a solution of *N*-(4-amino-2-phenylbenzoyl)methionine methyl ester hydrochloride (1.01 g, 2.05 mmol), prepared as in Example 192B, sodium acetate (0.425 g, 5.13 mmol) and acetic acid (0.205 g, 3.42 mmol) in isopropanol (7 mL). After 1 hour, Na(CN)BH₃ (0.147 g, 2.22 mmol) was added in two portions and the mixture was stirred for 15 hours before concentration under reduced pressure provided a waxy residue. Flash column chromatography (hexane-ethyl acetate-triethylamine 60:38:2) followed by radial chromatography eluting with 40% ethyl acetate-hexane) afforded the title compound (0.344 g, 31%) as a white foam. ¹H NMR (CDCl₃): δ 1.35-1.52 (comp, 18H), 1.52-1.71 (m, 1 H), 1.71-1.93 (m, 1 H), 2.02 (s, 3 H), 2.02-2.20 (comp, 2 H), 2.80-3.12 (comp, 2 H), 3.12-3.33 (br, 1 H), 3.33-3.50 (br, 1 H), 3.64 (s, 3 H), 3.83-4.28 (br, 3 H), 4.28-4.45 (br, 1 H), 4.60-4.72 (br, 1 H), 5.63-5.74 (br, 1 H), 6.44-6.58 (br, 1 H), 6.58-6.80 (br, 1 H), 7.33-7.52 (comp, 5 H), 7.72 (d, 1 H). LRMS (CI): 657 (M+1)⁺.

Example 286E

[4-(2-piperazinylmethylamino)-2-phenylbenzoyl]methionine

Sodium hydroxide (0.642 mL of a 0.979 M aqueous solution, 0.629 mmol) was added to a solution of the product of Example 286D (0.344 g, 0.524 mmol) in methanol (2 mL). After 5 hours the mixture was lyophilized, and the resulting white foam was treated with HCl (4.7 mL of a 4 M dioxane solution, 18.8 mmol). After 7 hours, pentane was added and the yellow precipitate was isolated by filtration to afford the desired compound (79.3 mg, 24%) as the bis-hydrochloride, mono-sodium chloride salt. ¹H NMR (300 MHz, CD₃OD) δ 1.71-1.85 (m, 1H), 1.91-2.00 (m, 1H), 2.02 (s, 3H), 2.02-2.15 (m, 1H), 2.15-2.27 (m, 1H), 3.32-3.56 (comp, 3H), 3.56-3.75 (comp, 4H), 3.75-3.96 (br, 2H), 4.45 (dd, 1H), 6.73 (s, 1H), 6.81 (d, 1H), 7.30-7.50 (comp, 6H). LRMS (CI) m/e 443 (M+H)⁺.



Example 302

[4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine lithium salt

7435

Example 302A4-(2-furylmethylaminomethyl)-2-phenylbenzoic acid methyl ester

To a stirred solution of 4-carboxaldehyde-2-phenylbenzoic acid methyl ester (0.73 g, 3.0 mmol), prepared as in Example 160B, in methanol (15 mL) was added furfurylamine (0.33 g, 3.4 mmol), sieves (~ 1g), NaBH₃CN (0.29 g, 4.6 mmol) and acetic acid (~0.3 mL) to pH = 6. The mixture was stirred for 3 hours at ambient temperature. The reaction was concentrated in vacuo and the residue was taken up in ethyl acetate and filtered through a short bed of silica gel. The bed was washed with ethyl acetate and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (CH₂Cl₂-ethyl acetate 9:1) to give the desired compound (0.72 g, 73%) as an opaque yellow paste.

7445

Example 302B[4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine methyl ester

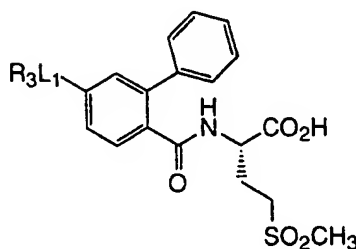
The desired compound was prepared by saponification of the product of Example 302A, followed by coupling with methionine methyl ester hydrochloride according to the method of Examples 299C and D.

7450

Example 302C[4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine methyl ester

To a stirred solution of the product of Example 302B (56 mg, 0.12 mmol) in THF (2 mL) was added a solution of LiOH·H₂O (5.5 mg, 0.13 mmol) in H₂O (1 mL) and the resulting solution stirred for 3 hours at ambient temperature. The reaction was concentrated in vacuo, diluted with H₂O, filtered and lyophilized to give the title compound (57 mg, 97%) as a white powder. ¹H NMR (300 MHz, DMSO-d₆, 90 °C) δ 7.48-7.24 (m, 9H), 7.07-7.04 (m, 1H), 6.37-6.34 (m, 1H), 6.24-6.20 (m, 1H), 3.76-3.69 (m, 5H), 2.43-2.16 (m, 3H), 2.00-1.66 (m, 5H). MS *m/z* 439 (M+ 1)⁺. Anal calcd for C₂₄H₂₅LiN₂O₄S·2 H₂O (480.50): C, 59.99; H, 6.08; N, 5.83. Found: C, 59.83; H, 5.83; N, 5.74.

7460



7465

Examples 350-357

All reactions were performed either in a Manual solid phase synthesis flask using a 120o rotary shaker or on an Advanced ChemTech Model 396 Multiple Peptide Synthesizer (Advanced ChemTech Inc.; Louisville, Kentucky) at ambient temperature.

7470 After the reactions were performed the finished compounds were cleaved from the resin. Usually, 80-90 mg of the dried resin containing the desired amide; urea; or secondary amine was treated with a 1.50 mL solution of 95/5 (v:v) trifluoroacetic acid/water for 1.5 h at ambient temperature. The spent resin was removed by filtration and the resulting cleavage solution evaporated in-vacuo. In most cases, 5- 20 mg of crude compound was obtained.

7475 Compounds obtained had the desired MW as determined by electrospray mass spectroscopy and had an HPLC purity of 40-90%, or were further purified by partition chromatography to afford compounds of 40-60% HPLC purity. Two types of gradients were used for the reverse phase HPLC. For the amides and ureas a gradient starting with 100% water-0.1% Trifluoroacetic acid and finishing with 100% acetonitrile-0.1% Trifluoracetic acid during a 30

7480 minute period was used. For the secondary amines a gradient beginning with 100% water-5mmol ammonium acetate and finishing with 80% acetonitrile-water-5mmol ammonium acetate during 25 minutes was used.

80 mg of resin (substitution 0.40 mmol/g) containing [4-amino-2-phenylbenzoyl]methionine-Wang-polystyrene resin was shaken for 3 min. with 1.0 mL. of

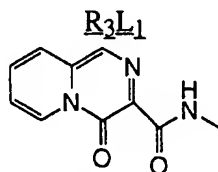
7485 N-methylpyrrolidone (NMP). The solvent was drained and the resin was treated 2x (3 min) with 1 mL. NMP. To the now swollen resin were then added 0.20 mL NMP; 0.20 mL of a 1.92 M diisopropylethylamine (DIEA)/NMP solution (15 eq.); 1.00 mL of a 0.180 mM/NMP solution of the desired carboxylic acid (5 eq.); and finally 0.20 mL of a 0.90 M Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrop; 5 equiv.)1/NMP

7490 solution. The reaction slurry was then mixed for 6 h and drained. The resin was then washed with NMP (3x; 1.0 mL; 3 min. ea.); isopropanol (IPA; 5x; 1.0 mL; 3 min. ea.); NMP (3x; 1.0 mL; 3 min. ea.); methanol (MEOH; 2x; 1.0 ml; 3 min. ea.); and finally diethyl ether (2x; 1.0 mL; 3 min. ea.). The resin was then dried and subjected to cleavage conditions described above.

7495

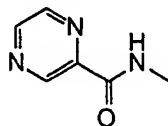
Example

354

MS (M+H)[±]

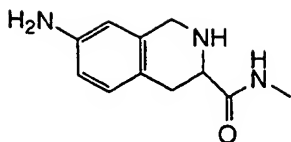
531

355

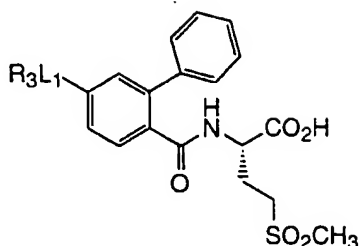


451

356



519

Examples 358

7500 90 mg of resin (substitution 0.39 mmol/g.) containing [4-amino-2-phenylbenzoyl]methionine-Wang-polystyrene resin was shaken with 1.0 mL dimethylformamide (DMF) for 3 min. The solvent was drained and the resin was then washed with DMF (3x; 1.0 mL; 3 min. ea.); tetrahydrofuran (THF; 4x; 1.0 mL; 3 min. ea.); THF/dichloromethane (DCM) 1:1 (v:v) (4x; 1.0 mL; 3 min. ea.). The resin was then treated

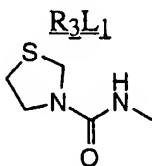
7505 with 0.20 mL of DCM/THF (1:1) and a 1.0 mL solution of 0.50 M p-Nitrophenylchloroformate/0.50 M DIEA in a 1:1 solvent mixture of DCM/THF. The resin suspension was then shaken for 15 min. and to the suspension was then added .020 mL of neat DIEA. After shaking for an additional 15 min.; the solvents were drained away and the resin was then washed with DCM/THF (1:1) (4x; 1.0 mL; 3 min. ea.) The resin was then

7510 treated with 0.20 mL of DMF and 1.0 mL of a DMF solution containing 0.50 M of the desired primary or secondary amine and 0.50 M of DIEA. The suspension was shaken for 30 min. The solvent was drained off and the resin was then washed with DMF (4x; 1.0 mL; 3 min. ea.); THF (4x; 1.0 mL; 3 min. ea.); DCM/THF (4x; 1.0 mL; 3 min. ea.); diethyl ether (4x; 1.0 mL; 3 min. ea.). The resin was then dried and subjected to cleavage from the resin

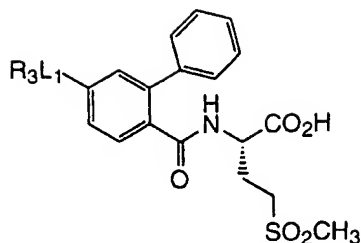
7515 as described above.

Example

358

MS (M+H)⁺

460



7520

Examples 360-362Examples 364-366Examples 369-374Examples 377-378Example 381

7525

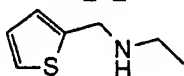
Typically 80 mg of resin (substitution of 0.40 mmol/g) containing 4-formyl-2-phenylbenzamide-L-Methionine-Wang-polystyrene resin was swollen with 1.0 mL of dimethyl acetamide (DMA) for 3 min. The solvent was drained and the resin was then washed with additional DMA (2x; 1.0 mL; 3 min. ea.). The resin was then suspended in 0.20 mL of DMA and to the suspension was then added a 1.0 mL solution containing 0.48 mM of the desired primary amine (10 eq.) in a 3:1 (v:v) solution of DMA/acetic acid. The resin was shaken for 2 h and was then treated with 0.25 mL of a 2.4 mM solution of sodium cyanoborohydride (10 eq.) in DMA. The resin-slurry was shaken for an additional 2 h. The solvents were drained and the resin was then washed with DMA (6x; 1.0 mL; 3 min. ea.); DMF (6x; 1.0 mL; 3 min. ea.); IPA (6x; 1.0 mL; 3 min. ea.); DMF (6x; 1.0 mL; 3 min. ea.); MEOH (6x; 1.0 mL; 3 min. ea.); diethyl ether (6x; 1.0 mL; 3 min. ea.). The resin was dried and then subjected to cleavage as described above.

7530

7535

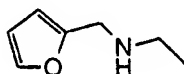
ExampleR₃L₁MS (M+H)[±]

360



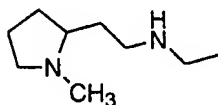
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361

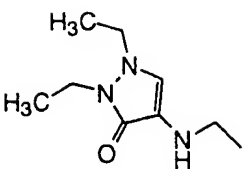
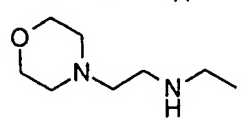
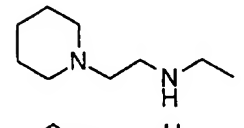
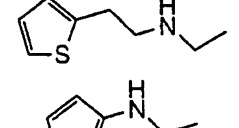
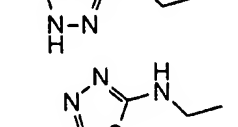
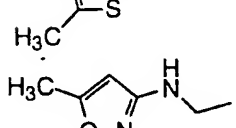
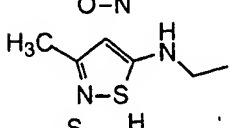
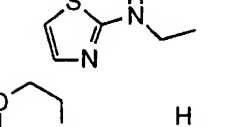
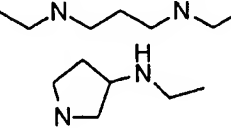
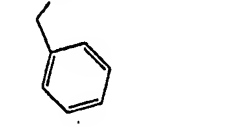
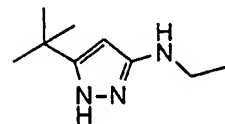
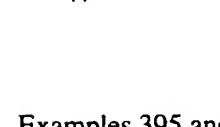


439

362



471

364		498
365		473
366		471
369		470
370		425
371		458
372		441
373		457
374		443
377		487
378		573
381		481

7540

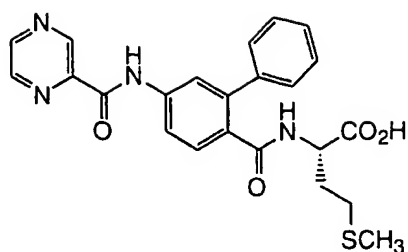
Examples 395 and Example 398

The following compounds were prepared using the materials and methods described above.

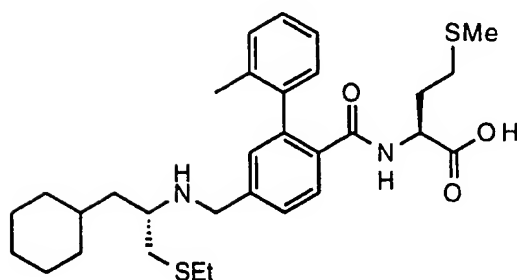
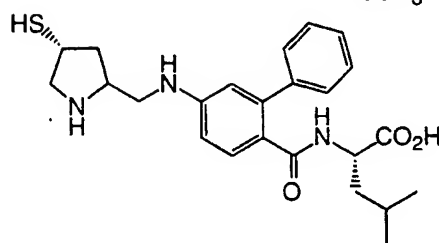
7545

Example

395



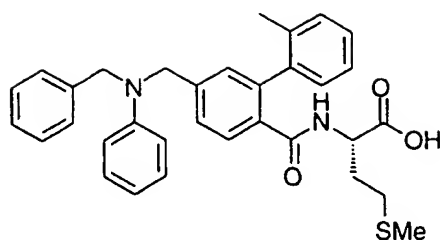
398

Example 403

7550 [4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl] methionine.

The desired compound was prepared according to the method of Example 349A except substituting (S)-(+)-1-ethylthio-3-cyclohexyl-2-propylamine hydrochloride for (S)-(+)-2-amino-3-cyclohexyl-1-propanol hydrochloride. ¹H NMR (DMSO-d₆, 300 MHz) δ 8.02 (m, 1H), 7.50-7.38 (m, 2H), 7.22-7.05 (m, 4H), 4.21 (m, 1H), 3.88-3.78 (m, 2H), 2.74-2.60 (m, 2H), 2.51 (s, 3H), 2.44 (q, J=7.5 Hz, 2H), 2.22-1.95 (m, 5H), 1.88-1.50 (m, 7H), 1.45-1.25 (m, 4H), 2.21-1.02 (m, 3H), 1.12 (t, J=7.5 Hz, 3H), 0.90-0.70 (m, 2H). MS (CI/NH₃) m/e: 557 (M+H)⁺ Anal calcd for C₃₁H₄₄N₂O₃S₂ • 1.15 H₂O: C, 64.47; H, 8.08; N, 4.85. Found: C, 64.48; H, 7.84; N, 4.72.

7560

Example 4064-(N-benzyl-N-phenyl)-aminomethyl-2-(2-methylphenyl)benzoylmethionine

7565 The desired compound was prepared according to Example 273 except substituting N-benzylaniline for 2-thiophenemethanol in Example 273A.

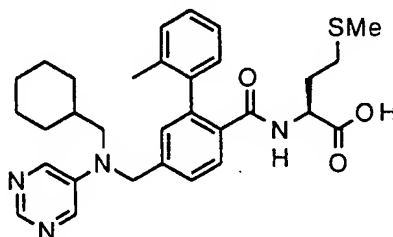
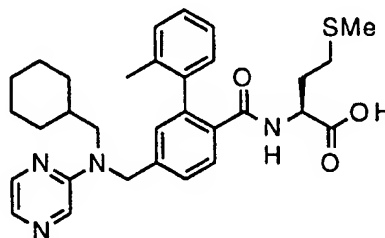
¹H NMR (CD₃OD): δ 1.62-1.77 (m, 1 H), 1.86-2.07 (comp, 7 H), 2.07-2.18 (comp, 2 H), 4.37-4.47 (br, 1 H), 4.70-4.84 (comp, 4 H), 6.68-6.89 (br, 3 H), 7.08-7.32 (comp, 13 H), 7.35-7.40 (m, 1 H), 7.56-7.62 (m, 1 H). LRMS (CI): 539 (M+1)⁺.

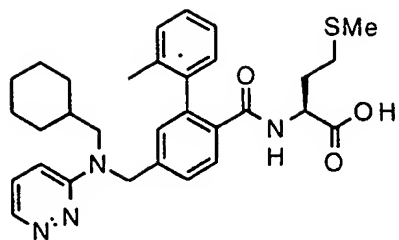
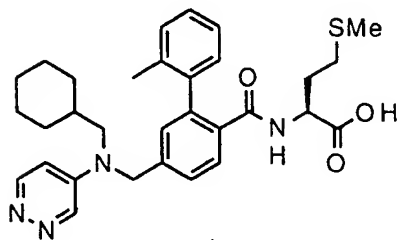
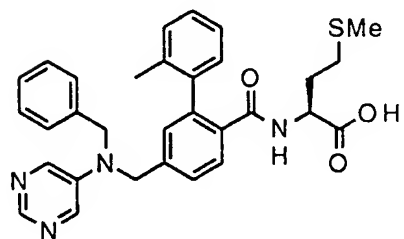
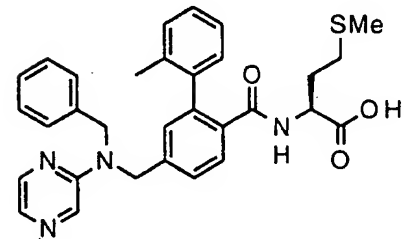
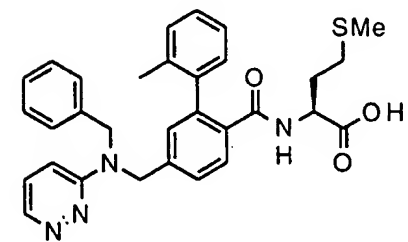
7570

Examples 411-417

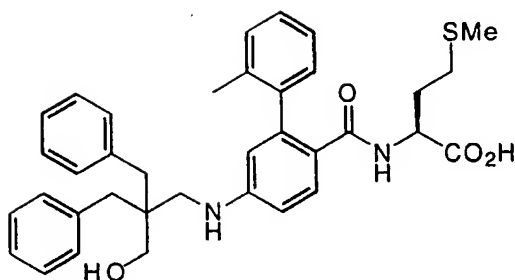
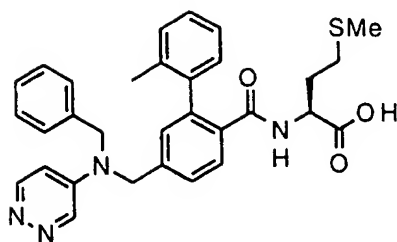
The following compounds are prepared according to the method of Example 407 except substituting the desired N-benzyl- or N-cyclohexylmethylaminopiperazine for N-benzyl-3-aminopyridine.

7575

411412

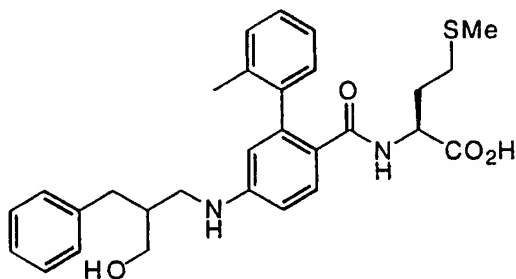
413414415416416A

417

Example 475

7580 N-[4-N-(2,2-dibenzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]methionine
sodium salt

The desired compound was prepared according to the method of Examples 25A -25B
¹H nmr (300 MHz, DMSO-d₆): δ 7.40 (d, 1 H), 7.25-7.10 (m, 15 H), 6.65 (m, 1 H), 6.27
 (d, 1 H), 6.08 (m, 1 H), 4.84 (m, 1 H), 3.70 (m, 1 H), 3.17 (br s, 2 H), 3.03 (br s, 2 H),
 7585 2.80 (AB q, 4 H), 2.18 (m, 1 H), 1.99,1.91 (2 br s's, 6 H), 1.97 (m, 1 H), 1.70-1.50 (m,
 2 H). MS (APCI +) m/e 597 (M+H)⁺.

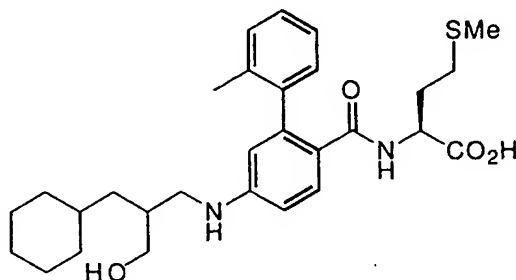
Example 476

7590 N-[4-N-(2-benzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]methionine
sodium salt

The desired compound was prepared according to the method of Examples 25A -25B
¹H nmr (300 MHz, DMSO-d₆): δ 7.35 (d, 1 H), 7.28-7.10 (m, 10 H), 6.50 (m, 1 H), 6.16
 7595 (d, 1 H), 6.05 (m, 1 H), 4.55 (m, 1 H), 3.64 (m, 1 H), 3.39 (m, 2 H), 2.62 (m, 2 H), 2.38

(m, 1 H), 2.15 (m, 1 H), 1.97, 1.91 (2 br s's, 6 H), 1.95 (m, 2 H), 1.70-1.50 (m, 2 H)
 (note: the methylene protons adjacent to the NH group might be buried in the residue water
 pk of DMSO). MS (APCI +) m/e 506 (M+H)⁺.

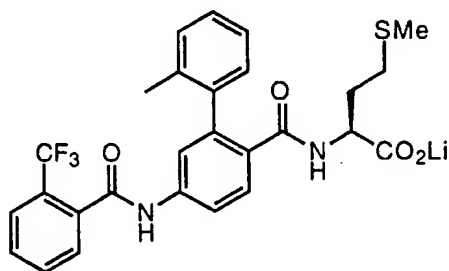
7600

Example 479

N-[4-N-(2-cyclohexylmethyl)-3-hydroxypropyl]amino-2-(2-
methylphenyl)benzoyl]methionine

7605 The desired compound was prepared according to the method of Examples 25A -25B
¹H nmr (300 MHz, DMSO-d₆): δ 7.37 (d, 1 H), 7.16 (m, 3 H), 7.02 (d, 1 H), 6.93 (m, 1
 H), 6.58 (m, 1 H), 6.00 (m, 1 H), 4.45 (m, 1 H), 3.65 (m, 1 H), 3.38 (m, 2 H), 2.19 (m,
 1 H), 2.03, 1.97, 1.93, 1.92 (4 s's, 6 H), 1.96 (M, 1 H), 1.90-0.75 (m's, 14 H). MS (ESI
 -): m/e 511 (M-H)⁻.

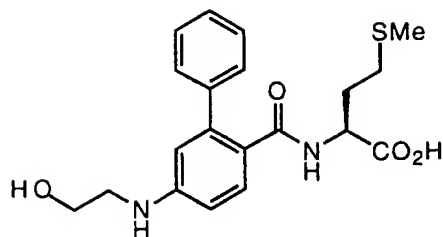
7610

Example 481

N-[4-N-(4-trifluoromethylnicotinoyl)amino-2-(2-methylphenyl)benzoyl]methionine
lithium salt

7615

The desired compound was prepared according to the method of Example 57. ¹H
 nmr (300 MHz, DMSO-d₆): δ 11.04 (br s, 1 H), 9.05 (s, 1 H), 8.98 (d, 1 H), 7.90 (d, 1
 H), 7.69 (br d, 1 H), 7.57 (m, 2 H), 7.23 (m, 4 H), 6.97 (m, 1 H), 3.70 (m, 1 H), 2.20
 (m, 1 H), 2.03 (m, 1 H), 1.91 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e
 7620 530 (M-H)⁻.

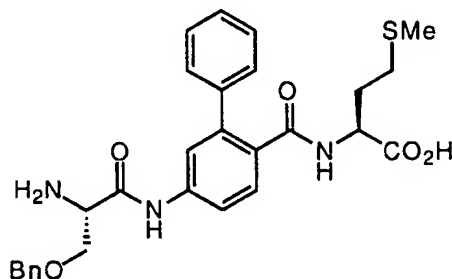
Example 502

7625

N-[4-N-2-hydroxyethylamino-2-phenylbenzoyl]methionine

The desired compound was prepared according to the method of Example 57, employing t-butyl bromoacetate. The resultant t-butyl ester was treated with TFA, and then reduced with borane. ¹H NMR (CD₃OD): δ 1.68-1.81 (m, 1 H), 1.89-2.10 (m, 1 H), 2.01 (s, 3 H), 2.02-2.24 (comp, 2 H), 3.28 (t, *J* = 5.9 Hz, 2 H), 3.72 (t, *J* = 5.9 Hz, 2 H), 4.44 (dd, *J* = 4.4, 9.2 Hz, 1 H), 6.57 (d, *J* = 2.3 Hz, 1 H), 6.65 (dd, *J* = 2.4, 8.5 Hz, 1 H), 7.28-7.44 (comp, 6 H). LRMS (CI): 389 (M+1)⁺

7630

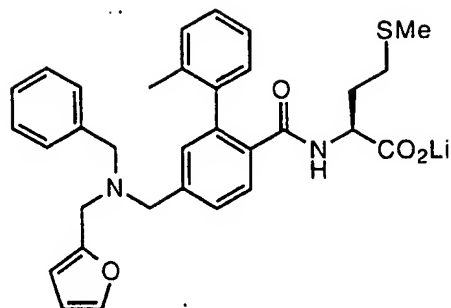
Example 503

7635

N-[4-(N-2-amino-3-benzyloxypropionyl)amino-2-phenylbenzoyl]methionine

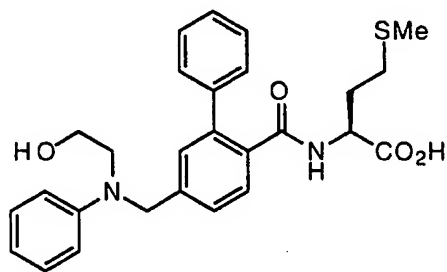
The desired compound was prepared according to the method of Example 57. ¹H NMR (CD₃OD): δ 1.71-1.88 (m, 1 H), 1.90-2.28 (comp, 6 H), 3.65-3.72 (m, 1 H), 3.86-3.94 (comp, 2 H), 4.24-4.31 (m, 1 H), 4.44-4.56 (m, 1 H), 4.62 (dd, *J* = 12.2, 29.2 Hz, 2 H), 7.23-7.58 (comp, 11 H), 7.62-7.70 (comp, 2 H). LRMS (CI): 522 (M+1 of free base)⁺

7640

Example 504

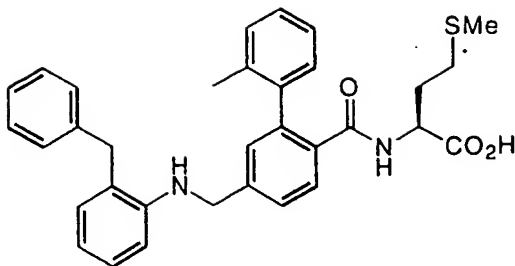
7645 N-[4-N-(furan-2-ylmethyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 158 ¹H NMR (CD₃OD): δ 1.57-1.70 (m, 1 H), 1.75-1.92 (comp, 2 H), 1.94-2.01 (comp, 6 H), 2.01-2.09 (br, 1 H), 3.56-3.67 (comp, 6 H), 4.17-4.29 (br, 1 H), 6.20-6.23 (m, 1 H),
 7650 6.33-6.36 (m, 1 H), 7.07-7.33 (comp, 8 H), 7.33-7.40 (comp, 2 H), 7.42-7.49 (comp, 2 H), 7.60-7.67 (m, 1 H). LRMS (CI): 543 (M+1 of protonated acid)⁺.

Example 505

N-[4-N-phenyl-N-benzylaminomethyl-2-phenylbenzoyl]methionine

The desired compound was prepared according to the method of Example 157 ¹H NMR (d₆-DMSO): δ 1.73-1.96 (comp, 2 H), 1.99 (s, 3 H), 2.12-2.32 (comp, 2 H), 5.53-3.66 (comp, 2 H), 3.72-3.76 (br s, 1 H), 4.24-4.33 (comp, 2 H), 4.57-4.61 (br s, 1 H),
 7660 4.72 (s, 2 H), 6.58-6.96 (comp, 3 H), 7.06-7.19 (comp, 2 H), 7.25-7.42 (comp, 8 H), 8.53 (d, J= 7.7 Hz, 1 H). LRMS (CI): 479 (M+1)⁺.

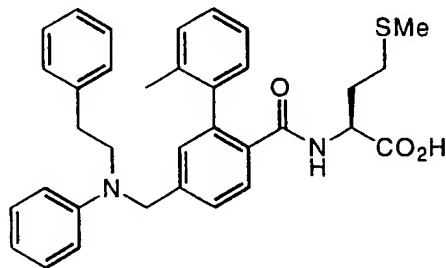


7665

Example 506N-[4-N-(2-benzylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 157 ¹H NMR (CD₃OD): δ 1.63-1.80 (br, 1 H), 1.87-2.07 (br, 7 H), 2.07-2.23 (comp, 2 H), 4.02 (s, 2 H), 4.38-4.51 (comp, 3 H), 6.87-6.93 (br, 1 H), 6.96-7.44 (comp, 14 H), 7.58-7.64 (m, 1 H). LRMS (CI): 539 (M+1)⁺, 556 (M+NH₄)⁺.

7670

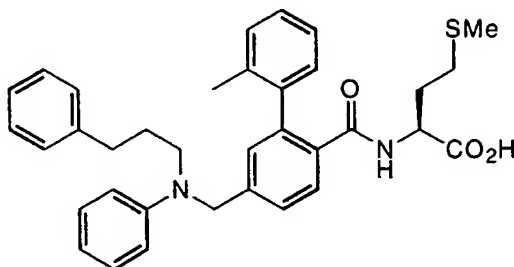
Example 507

7675

N-[4-N-(2-phenylethyl)-N-phenylaminomethyl-2-(2-methylphenyl)benzoyl]methionine

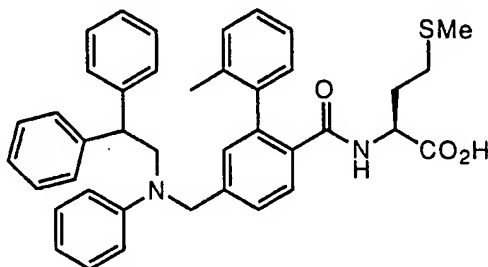
The desired compound was prepared according to the method of Example 157 ¹H NMR (CD₃OD): δ 1.55-1.68 (m, 1 H), 1.71-2.12 (comp, 9 H), 2.92 (t, 2 H), 3.63-3.71 (m, 2 H), 4.16-4.27 (br, 1 H), 4.52 (s, 2 H), 6.64 (t, 1 H), 6.74 (d, 2 H), 6.99-7.30 (comp, 13 H), 7.60 (d, 1 H). LRMS (ESI⁻): 551 (M-1)⁻.

7680

Example 508N-[4-N-(3-phenylpropyl)-N-phenylaminomethyl-2-(2-methylphenyl)benzoyl]methionine

7685 The desired compound was prepared according to the method of Example 157 ¹H NMR (CD₃OD): δ 1.45-1.62 (m, 1 H), 1.63-2.05 (comp, 11 H), 2.52-2.61 (m, 1 H), 3.30-3.39 (m, 2 H), 4.08-4.19 (br, 1 H), 4.50 (s, 2 H), 6.49-6.56 (comp, 3 H), 6.92-7.23 (comp, 13), 7.49-7.56 (m, 1 H). LRMS (ESI⁻): 565 (M-1)⁻.

7690

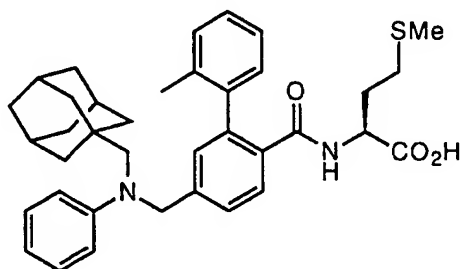


Example 509

N-[4-N-(2,2-diphenylethyl)-N-phenyl]aminomethyl-2-(2-methylphenyl)benzoyl]methionine

7695 The desired compound was prepared according to the method of Example 157 ¹H NMR (d₆-DMSO): δ 1.46-2.02 (comp, 10 H), 3.38-3.42 (m, 1 H), 3.61-3.73 (br, 1 H), 4.16 (d, *J* = 7.3 Hz, 2 H), 4.31 (s, 2 H), 4.40-4.47 (m, 1 H), 6.55-6.67 (comp, 3 H), 6.78 (s, 1 H), 6.82-6.94 (br, 1 H), 7.05-7.21 (comp, 8 H), 7.22-7.30 (comp, 4 H), 7.35-7.41 (comp, 5 H). LRMS (CI): 629 (M+1)⁺.

7700

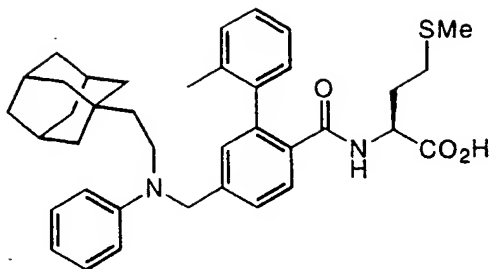


Example 510

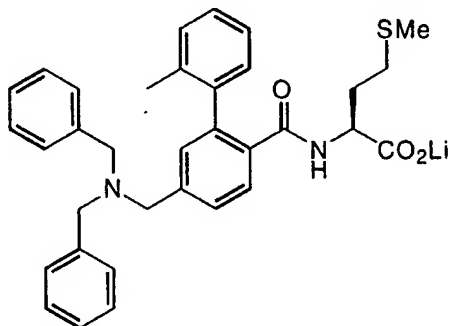
N-[4-N-(adamantan-1-ylmethyl)-N-phenyl]aminomethyl-2-(2-methylphenyl)benzoyl]methionine

7705 The desired compound was prepared according to the method of Example 157 ¹H NMR (d₆-DMSO): δ 1.48-2.20 (br, comp, 25 H), 3.16-3.31 (br m, 1 H), 3.40-4.30 (br comp, 4 H), 4.65-4.74 (br m, 1 H), 6.49-6.57 (br m, 1 H), 6.68-6.75 (br comp, 2 H), 6.85-7.12 (br comp, 3 H), 7.14-7.25 (br comp, 5 H), 7.45 (d, *J* = 8.0 Hz, 1 H). LRMS (CI): 597 (M+1)⁺.

7710

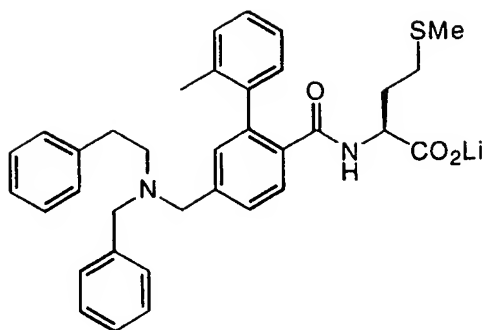
Example 511N-[4-N-(2-adamantan-1-ylethyl)-N-phenyl]aminomethyl-2-(2-methylphenyl)benzoyl]methionine

7715 The desired compound was prepared according to the method of Example 157 ¹H NMR (d₆-DMSO): δ 1.28-1.37 (comp, 2 H), 1.47-1.71 (comp, 15 H), 1.88-2.10 (comp, 11 H), 3.33-3.47 (br comp, 2 H), 3.61-3.69 (br m, 1 H), 4.54 (s, 2 H), 6.55 (t, *J*= 7.1 Hz, 1 H), 6.63 (d, *J*= 8.1 Hz, 2 H), 6.88-6.94 (br m, 1 H), 6.97 (d, *J*= 1.3 Hz, 1 H), 7.07-7.21 (comp, 5 H), 7.27 (dd, *J*= 1.7, 7.8 Hz, 1 H), 7.49 (d, *J*= 8.2 Hz, 1 H). LRMS (ESI⁻): 609 (M-1)⁻.

Example 512N-[4-N,N-dibenzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

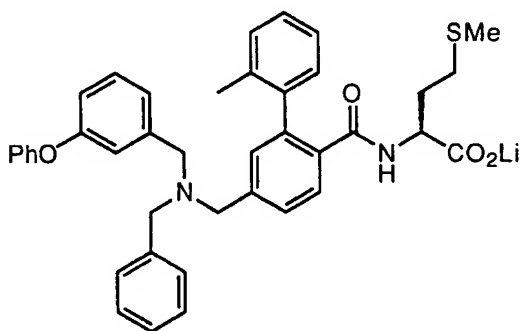
7725 The desired compound was prepared according to the method of Example 158 ¹H NMR (d₆-DMSO): δ 1.44-2.17 (comp, 10 H), 3.33-3.77 (comp, 7H), 6.90-7.56 (comp, 17 H). LRMS (ESI⁻): 551 (M-1 of protonated acid)⁻.

7730

Example 513

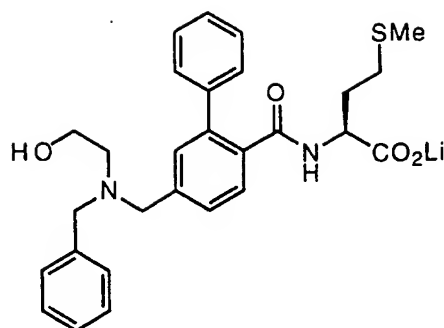
N-[4-N-(2-phenylethyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 158 ¹H NMR (d₆-DMSO): δ 1.65-1.90 (comp, 2 H), 1.96 (s, 3 H), 1.98-2.24 (comp, 5 H), 3.04-3.20 (comp, 4 H), 4.17-4.32 (br, 1 H), 4.36-4.56 (br, 4 H), 7.03-7.34 (comp, 12 H), 7.43-7.53 (br, 3 H), 7.54-7.63 (comp, 2 H), 7.67-7.76 (comp, 2 H), 7.76-7.84 (m, 1 H), 8.32 (d, *J* = 7.3 Hz, 1 H), 11.42-11.64 (br, 1 H), 12.35-12.55 (br, 1 H). LRMS (CI): 567 (M+1)⁺.

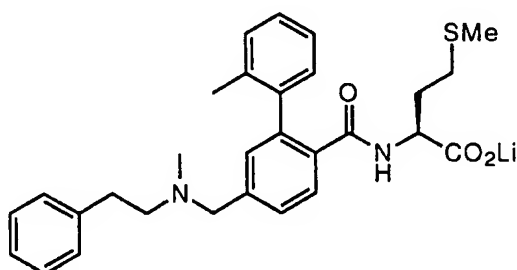
Example 514

N-[4-N-(3-phenoxybenzyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine
lithium salt

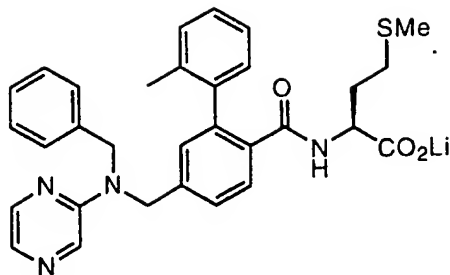
The desired compound was prepared according to the method of Example 158 ¹H NMR (d₆-DMSO): δ 1.65-1.90 (comp, 2 H), 1.95 (s, 3 H), 1.96-2.22 (comp, 5 H), 3.42-3.58 (br, 2 H), 4.15-4.39 (comp, 5 H), 6.88-7.62 (comp, 19 H), 7.64-7.71 (m, 1 H), 8.05-8.22 (m, 1 H), 11.30-11.44 (br, 1 H). LRMS (CI): 645 (M+1)⁺.

Example 515N-[4-N-(2-hydroxyethyl)-N-benzylaminomethyl]-2-phenylbenzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (d₆-DMSO): δ 1.75-1.97 (comp, 2 H), 2.00 (s, 3 H), 2.15-2.34 (comp, 2 H), 3.00-3.11 (br m, 2 H), 3.79-3.87 (br m, 2 H), 4.28-4.51 (comp, 5 H), 7.32-7.43 (comp, 3 H), 7.43-7.55 (comp, 6 H), 7.64-7.79 (comp, 4 H), 8.66 (d, J = 7.7 Hz, 1 H). LRMS (CI): 493 (M+1)⁺.

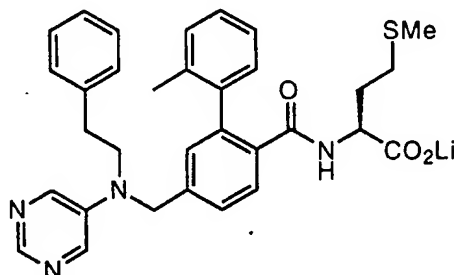
Example 516N-[4-N-methyl-N-(2-phenylethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (d₆-DMSO): δ 1.65-1.91 (comp, 2 H), 1.96 (s, 3 H), 1.99-2.28 (comp, 5 H), 2.75 (s, 1 H), 3.05-3.25 (comp, 2 H), 3.25-3.44 (comp, 2 H), 4.17-4.30 (br, 1 H), 4.30-4.40 (m, 1 H), 4.46-4.56 (m, 1 H), 7.07-7.38 (comp, 9 H), 7.47-7.60 (comp, 2 H), 7.68-7.75 (m, 1 H), 8.33 (d, J = 7.0 Hz, 1 H), 11.10-11.26 (br, 1 H), 12.50-12.86 (br, 1 H). LRMS (CI): 491 (M+1)⁺.

Example 517N-[4-N-benzyl-N-pyrazin-2-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

7780 The desired compound was prepared according to the method of Example 157 ¹H NMR (d₆-DMSO): δ 1.46-2.09 (comp, 10 H), 3.59-3.70 (br, 1 H), 4.83-4.95 (comp, 4 H), 6.90-6.95 (br, 1 H), 7.00 (s, 1 H), 7.04-7.34 (comp, 10 H), 7.49 (d, J = 8.1 Hz, 1 H), 7.80 (d, J = 2.6 Hz, 1 H), 8.04-8.05 (m, 1 H), 8.07-8.10 (m, 1 H). LRMS (ESI⁻): 539 (M-1 of protonated acid)⁻.

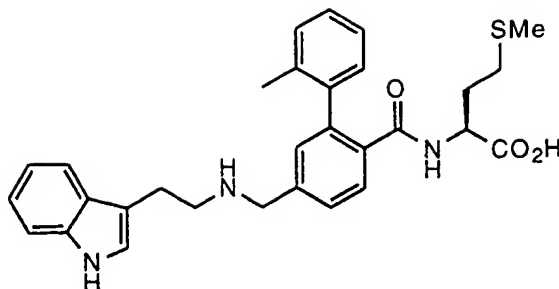
7785

Example 518N-[4-N-(2-phenylethyl)-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

7790

The desired compound was prepared according to the method of Example 157 ¹H NMR (d₆-DMSO): δ 1.46-2.05 (comp, 10 H), 2.88 (t, J = 7.5 Hz, 2 H), 3.56-3.65 (br, 1 H), 3.73 (t, J = 7.5 Hz, 2 H), 4.66 (s, 2 H), 6.90-7.01 (br comp, 2 H), 7.05-7.31 (comp, 10 H), 7.49 (d, J = 7.8 Hz, 1 H), 8.23 (s, 2 H), 8.41 (s, 1 H). LRMS (ESI⁻): 553 (M-1 of protonated acid)⁻.

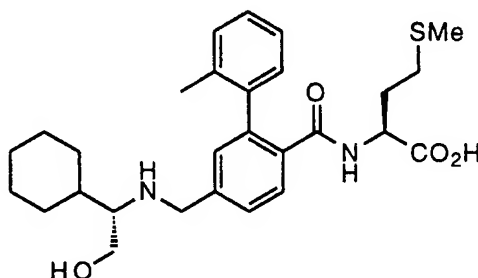
7795

**Example 519**

7800 N-[4-N-(2-indol-3-ylethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 1.48-1.75 (m, 2H), 1.75-1.97 (m, 3H), 1.93 (s, 3H), 1.99 (m, 2H), 2.06-2.15 (m, 2H), 2.74-2.87 (m, 4H), 3.65 (brs, 1H), 3.79 (m, 2H), 6.88-6.93 (m, 1H), 6.93 (ddd, $J=6.8, 6.8, 1.0$ Hz, 1H), 7.03 (ddd, $J=6.8, 6.8, 1$ Hz, 1H), 7.10 (d, $J=2.1$ Hz, 1H), 7.10-7.23 (m, 5H), 7.30 (d, $J=8$ Hz, 1H), 7.36 (dd, $J=8$ Hz, 1H), 7.46 (d, $J=7.8$ Hz, 1H), 7.47 (d, $J=7.8$ Hz, 1H). MS (ESI(+)) m/z 516 (M+H)⁺. Anal calcd for C₃₀H₃₂N₃O₃SLi•1.30H₂O: C, 66.11; H, 6.40; N, 7.71. Found: C, 66.15; H, 6.38; N, 7.64.

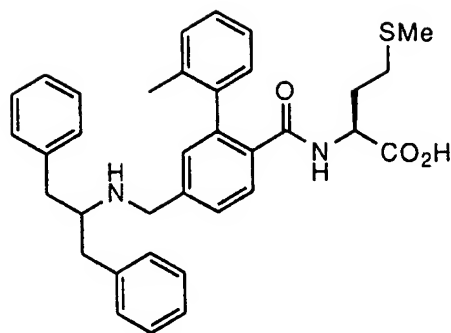
7810

**Example 520**

N-[4-N-(2-cyclohexyl-1-ethan-1-ol-2-yl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

7815 The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 0.93-1.19 (m, 6H), 1.35-1.77 (m, 4H), 1.77-2.06 (m, 7H), 1.91 (s, 3H), 2.18 (brs, 1H), 2.26 (m, 3H), 3.40-3.48 (m, 1H), 3.59-3.70 (m, 1H), 3.73 (d, $J=14.2$ Hz, 1H), 3.81 (d, $J=13.9$ Hz, 1H), 4.36 (brs, 1H), 6.87-7.00 (m, 1H), 7.11-7.27 (m, 5H), 7.36 (d, $J=8$ Hz, 1H), 7.47 (d, $J=8$ Hz, 1H). MS (ESI(+)) m/z 499 (M+H)⁺. Anal calcd for C₂₈H₃₇N₂O₄SLi•0.75H₂O: C, 64.91; H, 7.49; N, 5.41. Found: C, 64.92; H, 7.39; N, 5.21.

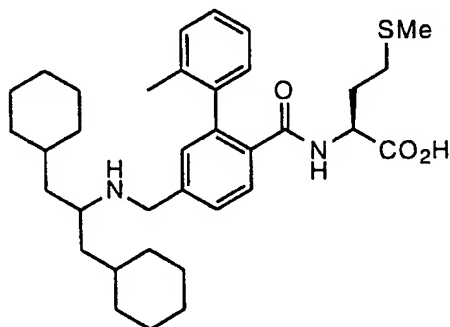
7820



Example 523

N-[4-N-(1,3-diphenylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 1.48-1.74 (m, 2H), 1.74-2.02 (m, 3H), 1.93 (s, 3H), 2.03-2.14 (m, 2H), 2.54-2.73 (m, 4H), 2.97 (pentet, $J=6.5$ Hz, 1H), 3.63-3.72 (brs, 1H), 3.78 (s, 2H), 6.90 (brs, 2H), 7.05-7.26 (m, 16H), 7.37 (d, $J=7.8$ Hz, 1H). MS (ESI(+)) m/z 567 (M+H)⁺. Anal calcd for C₃₅H₃₇N₂O₃SLi•0.90H₂O: C, 71.38; H, 6.64; N, 4.76. Found: C, 71.40; H, 6.28; N, 4.69.

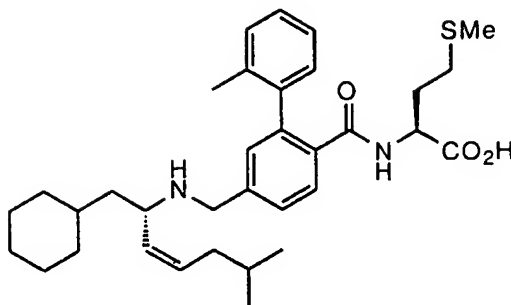


Example 524

N-[4-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 0.70-0.88 (m, 4H), 1.01-1.17 (m, 8H), 1.20-1.38 (m, 4H), 1.46-1.64 (m, 12H), 1.64-1.75 (m, 2H), 1.92 (s, 3H), 1.94-2.02 (m, 2H), 2.13-2.18 (m, 2H), 3.60-3.76 (m, 3H), 6.84-6.97 (m, 1H), 7.04-7.24 (m, 5H), 7.36 (dd, $J=8$, 1 Hz, 1H), 7.45 (d, $J=8$ Hz, 1H). MS (ESI(+)) m/z 579 (M+H)⁺. Anal calcd for

7845 $C_{35}H_{49}N_2O_3SLi \cdot 0.75H_2O$: C, 70.26; H, 8.51; N, 4.68. Found: C, 70.25; H, 8.52; N, 4.57.



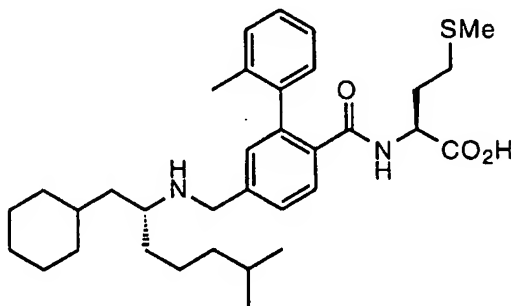
7850

Example 526

N-[4-N-(1-Cyclohexyl-6-methylhept-3-en-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158 1H NMR (300 MHz, DMSO) δ 1.74-0.86 (m, 7H), 1.02-1.19 (m, 4H), 1.27-1.38 (m, 2H),
 7855 1.46-1.87 (m, 14H), 1.93 (s, 3H), 1.99 (s, 3H), 2.17 (m, 1H), 3.51-3.82 (m, 3H), 5.11 (m, 1H), 5.43 (m, 1H), 6.83-6.96 (m, 1H), 7.00-7.24 (m, 5H), 7.24-7.36 (m, 1H), 7.47 (d, $J=7$ Hz, 1H). MS (APCI(+)) m/z 565 ($M+H$) $^+$. Anal calcd for $C_{34}H_{47}N_2O_3SLi \cdot 2.02H_2O$: C, 67.20; H, 8.48; N, 4.61. Found: C, 67.24; H, 8.35; N, 4.47.

7860

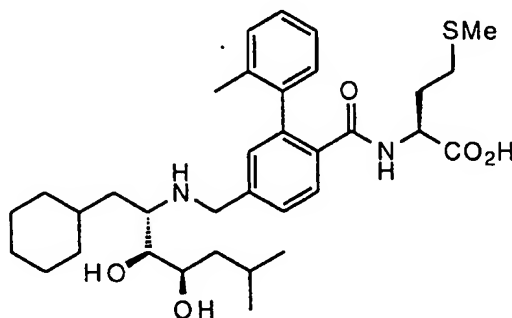
Example 527

N-[4-N-(1-Cyclohexyl-6-methylheptan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

7865

The desired compound was prepared according to the method of Example 158 1H NMR (300 MHz, DMSO) δ 0.80 (d, $J=5$ Hz, 3H), 0.82 (d, $J=5$ Hz, 3H), 1.02-1.40 (m, 12H), 1.40-1.65 (m, 12H), 1.75-1.83 (m, 1H), 1.92 (s, 3H), 1.99 (m, 1H), 2.16 (m, 1H),

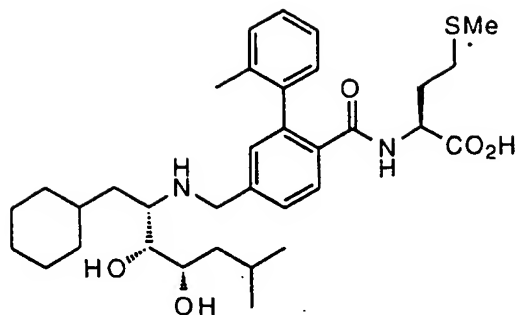
2.43 (m, 1H), 3.60-3.77 (m, 3H), 6.86-6.95 (m, 1H), 7.08-7.22 (m, 5H), 7.35 (d, $J=8.0$ Hz, 1H), 7.47 (d, $J=8.0$ Hz, 1H). MS (APCI(+)) m/z 567 ($M+H$)⁺. Anal calcd for $C_{34}H_{49}N_2O_3SLi \cdot 1.15H_2O$: C, 66.99; H, 8.48; N, 4.60. Found: C, 67.03; H, 8.62; N, 4.49.



Example 528

N-[4-N-(1-Cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

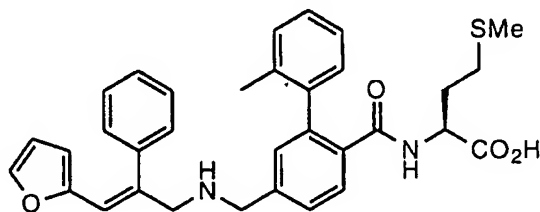
The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 0.72-1.35 (m, 10H), 0.85 (d, $J=7$ Hz, 3H), 0.87 (d, $J=7$ Hz, 3H), 1.43-1.76 (m, 6H), 1.82-2.14 (m, 4H), 2.00 (s, 3H), 2.06 (s, 3H), 3.07 (brs, 1H), 3.58 (s, 1H), 3.96-4.14 (m, 2H), 4.40-4.59 (m, 2H), 4.99-5.23 (m, 4H), 6.08-6.10 (m, 1H), 7.17-7.35 (m, 5H), 7.55 (m, 1H), 7.74 (m, 1H), 8.80 (brs, 0.5H), 9.25 (brs, 0.5H). MS (DCI/NH₃) m/z 599 ($M+H$)⁺. Anal. calcd for $C_{34}H_{50}N_2O_5S \cdot 1.55H_2O \cdot 1.05TFA$: C, 55.70; H, 6.90; N, 3.51. Found: C, 55.72; H, 6.91; N, 3.38.

Example 529

7890 N-[4-N-(1-Cyclohexyl)-2,3-dihydroxy-6-methylheptan-2-yl]
aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 0.80-1.40 (m, 16H), 1.45-1.77 (m, 6H), 2.00 (s, 3H), 2.04 (s, 3H), 1.80-2.13 (m, 4H), 3.20-3.40 (m, 1H), 3.59 (m, 1H), 3.39-4.10 (m, 1H), 4.38-4.55 (m, 1H), 4.60-4.90 (m, 4H), 6.10 (m, 1H), 7.20-7.40 (m, 5H), 7.55 (m, 1H), 7.80 (m, 1H), 9.0 (brs, 1H). MS (DCI/NH₃) m/z 599 (M+H)⁺. Anal calcd for C₃₄H₅₀N₂O₅S•1.00H₂O•1.85TFA: C, 54.70; H, 6.56; N, 3.38. Found: C, 54.70; H, 6.59; N, 3.27.

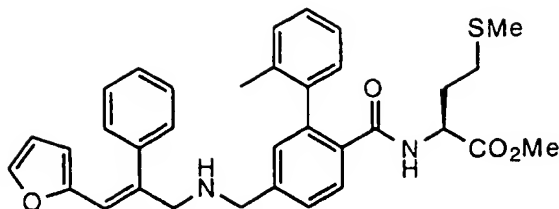
7900

Example 537

N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine lithium salt

7905 The desired compound was prepared according to the method of Examples 158 ¹H NMR (MeOH-*d*₄) δ 7.69-7.61 (m, 1 H), 7.40-7.29 (m, 3 H), 7.22-7.17 (m, 9 H), 6.70 (dd, 1 H, J = 8.7, 2.6 Hz), 6.48 (bs, 1 H), 6.41-6.38 (m, 1 H), 6.15-6.13 (m, 1 H), 5.44 (d, 1 H, J = 3.4 Hz), 4.46-4.38 (m, 1 H), 4.10 (d, 2 H, J = 1.3 Hz), 2.18-1.85 (m, 8 H), 1.79-1.66 (m, 1 H), 1.59-1.52 (m, 1 H); MS m/z 541 (M⁺ + 1, 100).

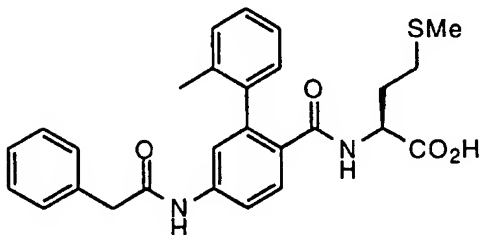
7910

**Example 538****N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester**

7915

The desired compound was prepared according to the method of Example 158 ¹H NMR (CDCl₃) δ 7.93 (dd, 1 H, *J* = 17.7, 8.6 Hz), 7.42-7.27 (m, 6 H), 7.22-7.19 (m, 4 H), 6.67 (dd, 1 H, *J* = 8.8, 2.4 Hz), 6.52 (bs, 1 H), 6.33 (d, 1 H, *J* = 2.4 Hz), 6.15 (dd, 1 H, *J* = 3.4, 1.7 Hz), 5.70 (t, 1 H, *J* = 8.7 Hz), 5.52 (d, 1 H, *J* = 3.4 Hz), 4.62-4.55 (m, 1 H), 4.30-4.27 (m, 1 H), 4.14-4.11 (m, 2 H), 3.63 (s, 3 H), 2.18-2.00 (m, 8 H), 1.88-1.76 (m, 1 H), 1.56-1.48 (m, 1 H); MS *m/z* 555 (*M*⁺ + 1, 100).

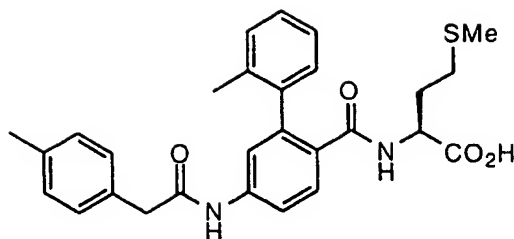
7920

**Example 540****N-[4-N-phenylacetyl-amino-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Example 57 ¹H NMR (DMSO-*d*₆) δ 10.42 (s, 1 H), 7.60 (d, 1 H, *J* = 8.5 Hz), 7.51 (d, 1 H, *J* = 8.5 Hz), 7.47 (bs, 1 H), 7.34-7.28 (m, 3 H), 7.25-7.16 (m, 6 H), 6.97-6.85 (m, 1 H), 3.68-3.65 (m and s, 3 H total), 2.15-1.85 (m, 8 H), 1.78-1.64 (m, 1 H), 1.59-1.51 (m, 1 H); MS *m/z* 477 (*M*⁺ + 1, 100).

7925

7930

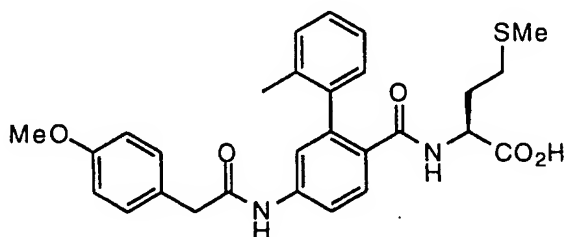


7935

Example 541N-[4-N-(4'-methylphenylacetyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

7940

The desired compound was prepared according to the method of Example 57 ¹H NMR (DMSO-*d*₆) δ 10.40 (s, 1 H), 7.60 (d, 1 H, *J* = 7.9 Hz), 7.51 (d, 1 H, *J* = 8.5 Hz), 7.46 (bs, 1 H), 7.22-6.83 (m, 9 H), 3.71-3.62 (m, 1 H), 3.60 (s, 2 H), 2.27 (s, 3 H), 2.23-1.86 (m, 8 H), 1.71-1.64 (m, 1 H), 1.60-1.52 (m, 1 H); MS *m/z* 491 (*M*⁺ + 1, 100).

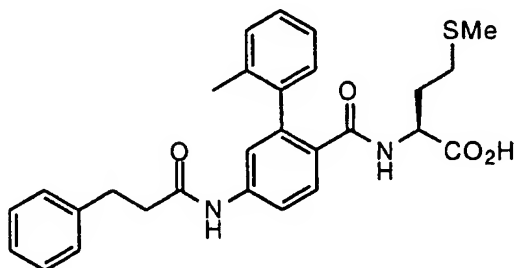


7945

Example 542N-[4-N-(4'-methoxyphenylacetyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

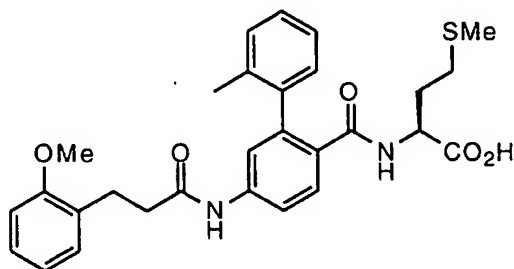
7950

The desired compound was prepared according to the method of Example 57 ¹H NMR (DMSO-*d*₆) δ 7.67-7.63 (m, 2 H), 7.50-7.45 (m, 1 H), 7.26-7.09 (m, 6 H), 6.89-6.85 (m, 2 H), 6.81-6.77 (m, 1 H), 4.24-4.20 (m, 1 H), 3.77 and 3.74 (2s, 3 H total), 3.62 and 3.39 (2s, 2 H total), 2.23-1.95 (m, 8 H), 1.89-1.78 (m, 1 H), 1.66-1.59 (m, 1 H); MS *m/z* 507 (*M*⁺ + 1, 100).

Example 543

7955 N-[4-N-(3-phenylpropionyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

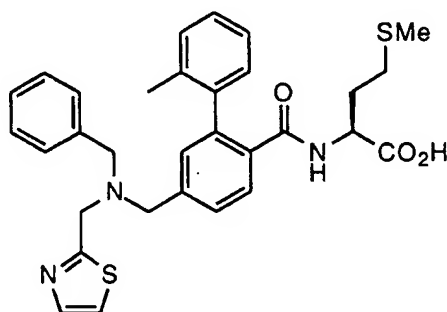
The desired compound was prepared according to the method of Example 57 ¹H NMR (DMSO-*d*₆) δ 10.17 (bs, 1 H), 7.60 (d, 1 H, *J* = 7.9 Hz), 7.51 (d, 1 H, *J* = 8.6 Hz), 7.45 (bs, 1 H), 7.29-6.85 (m, 10 H), 3.71-3.65 (m, 1 H), 2.90 and 2.69 (2t, 2 H total, *J* = 7.9 Hz), 2.64 and 2.15 (2t, 2 H total, *J* = 7.9 Hz), 2.17-1.83 (m, 8 H), 1.71-1.64 (m, 1 H), 1.59-1.53 (m, 1 H); MS *m/z* 491 (*M*⁺ + 1, 100).



Example 544

7965 N-[4-N-(3-(2-methoxyphenyl)propionyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 57 ¹H NMR (DMSO-*d*₆) δ 10.10 (bs, 1 H), 7.59 (d, 1 H, *J* = 7.9 Hz), 7.50 (d, 1 H, *J* = 8.6 Hz), 7.45 (bs, 1 H), 7.22-7.09 (m, 6 H), 6.96 (d, 1 H, *J* = 7.9 Hz), 6.89-6.79 (m, 3 H), 3.78 and 3.76 (2s, 3 H total), 2.86 and 2.69 (2t, 2 H total, *J* = 7.9 Hz), 2.59 and 2.07 (2t, 2 H total, *J* = 7.9 Hz), 2.17-1.84 (m, 8 H), 2.71-2.63 (m, 1 H), 1.58-1.53 (m, 1 H); MS *m/z* 521 (*M*⁺ + 1, 100).



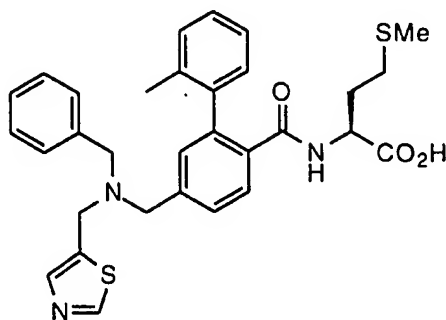
7975

Example 548

N-[4-N-benzyl-N-(thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO *d*₆): δ 8.09, d, 1H; 7.72, d, 1H; 7.66, d, 1H; 7.50, m, 2H; 7.38,

7980 m, 4H; 7.23, m, 4H; 7.14, m, 2H; 4.20, ddd, 1H; 3.89, s, 2H; 3.70, s, 2H; 3.68, s, 2H; 2.09, m, 4H; 1.96, s, 3H; 1.63 - 1.90, m, 2H. MS (APCI(+)) 560 (MH⁺). Calc'd for C₃₁H₃₃N₃O₃S₂•0.32 H₂O: C 65.84, H 6.00, N 7.43: Found: C 65.85, H 5.75, N 7.34



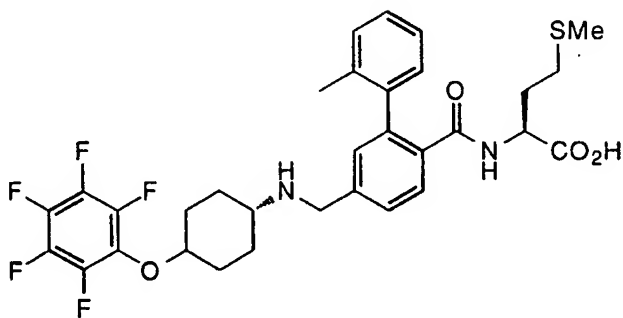
7985

Example 549

N-[4-N-benzyl-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 12.45, bs, 1H; 9.03, s, 1H; 8.12, d, 1H; 7.79, s, 1H; 7.48, dd, 2H; 7.35, m, 4H; 7.04 - 7.28, m, 6H; 4.21, ddd, 1H; 3.81, s, 2H; 3.61, s, 2H; 3.58, s, 1H; 1.98 - 2.21, 5H; 1.96, s, 3H; 1.61 - 1.89, m, 2H. MS (APCI(+)) 560 (MH⁺). Calc'd for C₃₁H₃₃N₃O₃S₂•0.78 H₂O: C 64.89, H 6.07, N 7.32: Found: C 64.89, H 5.71, N 7.29

7995

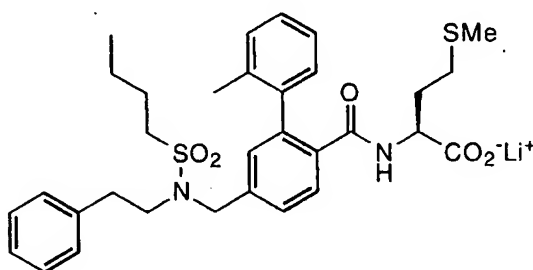


Example 596

N-[4-N-(4-trans-pentafluorophenoxy)cyclohexylaminomethyl-2-(2-methylphenyl)benzoyl]methionine

8000 A solution of *trans*-4-aminocyclohexanol (3.03 g, 20.0 mmol) and diisopropylethylamine (7.4 mL, 42.0 mmol) in methylene chloride (30 mL) was treated with *t*-butyl dicarbonate (4.37 g, 20.0 mmol) over 5 minutes. The reaction stirred overnight at room temperature and was washed with 1 M HCl, 5% NaHCO₃, and brine to give the Boc-

amine in nearly quantitative yield. A portion of this product (215 mg, 1.0 mmol) was
 8005 combined with hexafluorobenzene (223 mg, 1.2 mmol) and 15-crown-5 (44 mg, 0.2 mmol)
 in DMF (3 mL) at room temperature. NaH (60% in oil, 4.4 mg, 1.2 mmol) was added and
 stirred overnight. Standard aqueous workup provided 149 mg of the protected
 pentafluorophenyl ether which was treated with excess TFA in methylene chloride, stripped
 to dryness, and reductively alkylated and saponified in a manner analogous to Example 158
 8010 to provide 160 mg of the title compound. MS m/e 635 (M-H)⁻. ¹H NMR (CDCl₃, 300
 MHz) δ 1.5 (m, 4H), 1.79 (m, 1H), 2.05 (m, 12H), 2.81 (m, 1H), 4.05 (m, 4H), 6.25 (m,
 1H), 6.81 (m, 2H), 7.1-7.7 (m, 7H).

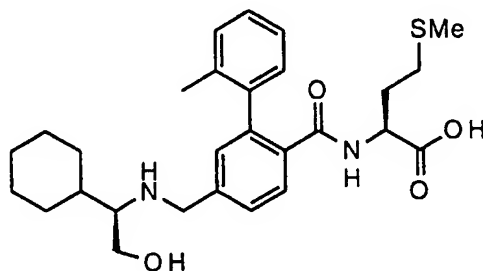


8015

Example 598*N*-[4-(*N*-2-phenethyl-*N*-butanesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

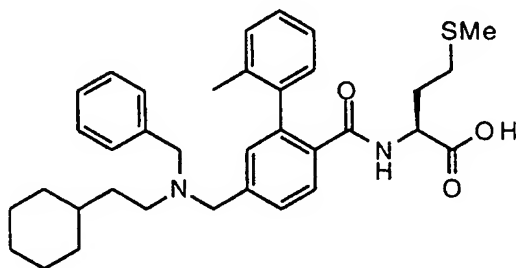
8020 The desired compound was prepared according to the method of Example 157. ¹H
 (300MHz, DMSO-d₆, δ) 7.62 (1H, d, J=7Hz), 7.52 (1H, dd, J=7&2Hz), 7.20-7.10 (10H,
 m), 7.14 (1H, bd, J=7Hz), 4.65 (2H, bs), 3.76 (1H, m), 3.00 (2H, m), 2.78 (2H, m),
 2.25-2.00 (5H, m), 1.99 (3H, s), 1.90-1.70 (4H, m), 1.62 (2H, m), 1.37 (2H, m), 0.92
 (3H, t, J=8Hz). m/e (ESI) 595 (MH)⁻ Anal.calc. for C₃₂H₃₉LiN₂O₅S₂·0.50 H₂O C

8025 62.83, H 6.59, N 4.38 Found C 62.59, H 6.59, N 4.44

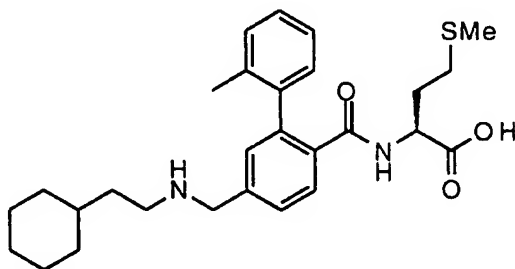
Example 604

N-[4-(2-cyclohexylethan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionineLithium Salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (DMSO-d₆, 300 MHz) δ 7.48 (d, *J*=8 Hz, 1H), 7.37 (dd, *J*=8, 1 Hz, 1H), 7.20-7.08 (m, 4H), 6.90 (m, 1H), 4.40 (t, *J*=5 Hz, 1H), 3.82-3.65 (m, 3H), 3.46 (m, 1H), 3.31 (m, 1H), 2.28-2.12 (m, 2H), 2.02-1.80 (m, 7H), 1.77-1.37 (m, 8H), 1.18-0.92 (m, 5H); Anal. Calcd for C₂₈H₃₇LiN₂O₄S•1.35 H₂O: C, 63.58; H, 7.57; N, 5.30. Found: C, 63.55; H, 7.31; N, 4.89.

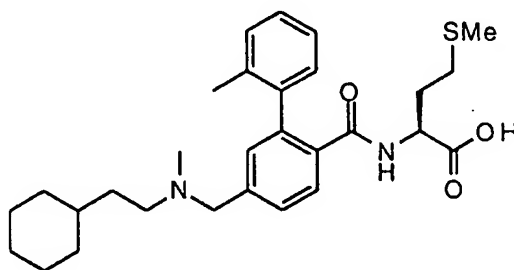
Example 605N-[4-(N-benzyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionineLithium Salt

The desired compound was prepared according to the method of Example 158. MS (Cl/NH₃) *m/z*: (M-H)⁻ 571; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.50 (d, *J*=8 Hz, 1H), 7.38-7.12 (m, 10H), 6.92 (d, *J*=6 Hz, 1H), 3.69 (m, 1H), 3.56 (s, 2H), 3.53 (s, 2H), 2.38 (t, *J*=7 Hz, 2H), 2.15-1.95 (m, 4H), 1.91 (s, 3H), 1.58-1.42 (m, 7H), 1.38-1.02 (m, 7H), 0.81-0.68 (m, 2H); Anal. Calcd for C₃₅H₄₃LiN₂O₃S•1.75 H₂O: C, 68.89; H, 7.68; N, 4.59. Found: C, 68.85; H, 7.44; N, 4.37.

Example 607

N-[4-(N-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine
Trifluoroacetate Salt

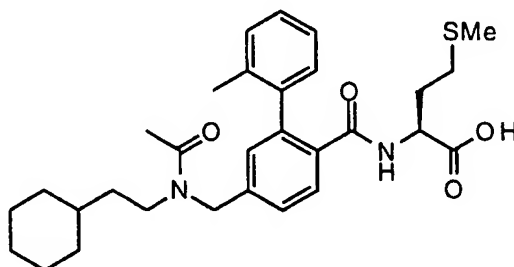
8055 The desired compound was prepared according to the method of Example 158. MS
 (CI/NH₃) m/z: (M+H)⁺ 483; ¹H NMR (DMSO-d₆, 300 MHz) δ 8.09 (m, 1H), 7.49-7.42
 (m, 2H), 7.26 (m, 1H), 7.16-6.98 (m, 3H), 4.14 (m, 1H), 4.11 (s, 2H), 2.87-2.80 (m,
 2H), 2.11-1.90 (m, 5H), 1.86 (s, 3H), 1.78-1.47 (m, 7H), 1.45-1.37 (m, 2H), 1.26-1.00
 (m, 4H), 0.87-0.72 (m, 2H); Anal. Calcd for C₂₈H₃₈N₂O₃S•C₂HF₃O₂•1.45 H₂O: C,
 8060 57.76; H, 6.93; N, 4.49. Found: C, 57.69; H, 6.51; N, 4.48.



Example 608

8065 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine
Lithium Salt

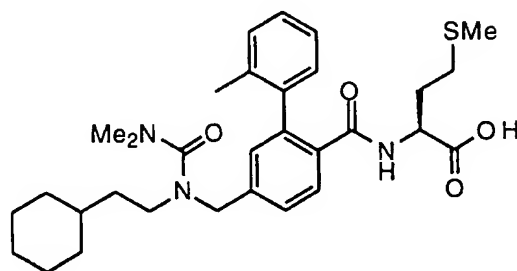
The desired compound was prepared according to the method of Example 158. MS
 (CI/NH₃) m/z: (M+H)⁺ 497; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.49 (d, J=8 Hz, 1H),
 7.32 (dd, J=8, 1 Hz, 1H), 7.25-7.06 (m, 4H), 6.93 (d, J=6 Hz, 1H), 3.73-3.64 (m, 1H),
 8070 3.49 (s, 2H), 2.32 (t, J=7 Hz, 2H), 2.15 (m, 1H), 2.12 (s, 3H), 2.06-1.80 (m, 3H), 1.92
 (s, 3H), 1.74-1.50 (m, 7H), 1.35-1.05 (m, 7H), 0.90-0.76 (m, 2H); Anal. Calcd for
 C₂₉H₃₉LiN₂O₃S•1.05 H₂O: C, 66.78; H, 7.94; N, 5.37. Found: C, 66.81; H, 7.75; N,
 5.07.



Example 609

N-[4-(N-acetyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
Lithium Salt

8080 The desired compound was prepared according to the method of Example 607. The resultant amine was reacted with acetic anhydride - lithium carbonate under Schotten-Baumann conditions. MS (CI/NH₃) m/z: (M-H)⁻ 523; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.59 minor conformer 7.53 major conformer (d, J=8 Hz, 1H), 7.31 (d, J=8 Hz, 1H), 7.25-7.14 (m, 3H), 7.07-6.96 (m, 2H), 4.63 minor conformer 4.57 major conformer (s, 2H),
 8085 3.80 (m, 1H), 3.33-3.25 (m, 2H), 2.21-1.85 (m, 10H), 1.77-1.56 (m, 7H), 1.44-1.30 (m, 3H), 1.25-1.07 (m, 4H), 0.95-0.83 (m, 2H); Anal. Calcd for C₃₀H₃₉LiN₂O₄S•1.45 H₂O: C, 64.72; H, 7.59; N, 5.03. Found: C, 64.75; H, 7.40; N, 4.71.



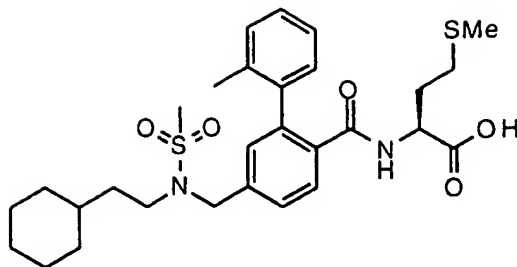
8090

Example 610

N-[4-(N-(N,N-dimethylaminocarbonyl)-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

8095 The compound resulting from Example 607 was treated with dimethyl carbamoyl chloride under Schotten-Baumann conditions to yield the title compound. MS (CI/NH₃) m/z: (M+H)⁺ 554; ¹H NMR (DMSO-d₆, 300 MHz) δ 8.18 (d, J=8 Hz, 1H), 7.54 (d, J=8 Hz, 1H), 7.38 (dd, J=8, 2 Hz, 1H), 7.29-7.13 (m, 4H), 4.40 (s, 2H), 4.28 (m, 1H), 3.13-3.06 (m, 2H), 2.80 (s, 6H), 2.29-2.06 (m, 5H), 2.02 (m, 3H), 1.94-1.62 (m, 6H), 1.47-1.15 (m, 7H), 0.96-0.84 (m, 2H); Anal. Calcd for C₃₁H₄₃N₃O₄S•0.45 H₂O: C, 66.27; H, 7.88; N, 7.48. Found: C, 66.37; H, 8.10; N, 6.88.

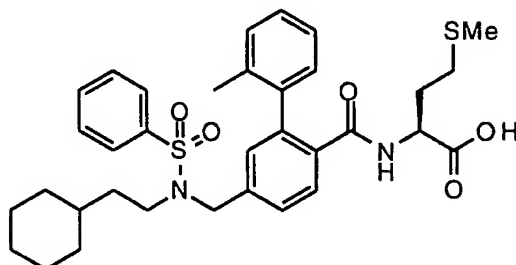
8100

Example 611

8105 N-[4-(N-(2-cyclohexylethyl)-N-methanesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

The compound resulting from Example 607 was treated with methanesulfonyl chloride under Schotten-Baumann conditions to yield the title compound. MS (CI/NH₃) m/z: (M-H)⁻ 559; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.54 (d, J=8 Hz, 1H), 7.41 (d, J=8 Hz, 1H), 7.25-7.13 (m, 4H), 6.97 (d, J=7 Hz, 1H), 4.36 (s, 2H), 3.67 (m, 1H), 3.17-3.12 (m, 2H), 2.96 (s, 3H), 2.17-1.91 (m, 6H), 1.70-1.48 (m, 9H), 1.31-1.04 (m, 6H), 0.82-0.69 (m, 2H); Anal. Calcd for C₂₉H₃₉LiN₂O₅S₂•2.75 H₂O: C, 56.52; H, 7.28; N, 4.55. Found: C, 56.72; H, 6.49; N, 3.92.

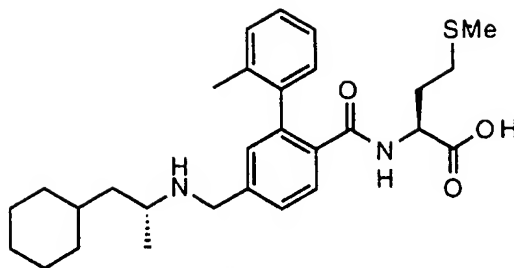
8115

Example 612

N-[4-(N-benzenesulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

8120 The compound resulting from Example 607 was treated with benzenesulfonyl chloride under Schotten-Baumann conditions to yield the title compound. MS (CI/NH₃) m/z: (M-H)⁻ 621; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.86 (m, 1H), 7.72-7.59 (m, 4H), 7.51 (d, J=8 Hz, 1H), 7.36 (m, 1H), 7.26-7.07 (m, 4H), 6.96 (d, J=6 Hz, 1H), 4.36 (s, 2H), 3.66 (m, 1H), 3.10 (m, 2H), 2.16-1.92 (m, 5H), 1.70-1.40 (m, 7H), 1.30-0.99 (m, 6H), 0.90-0.61 (m, 5H); Anal. Calcd for C₃₄H₄₁LiN₂O₅S₂•1.25 H₂O: C, 62.70; H, 6.73; N, 4.30. Found: 63.10; H, 6.72; N, 3.52.

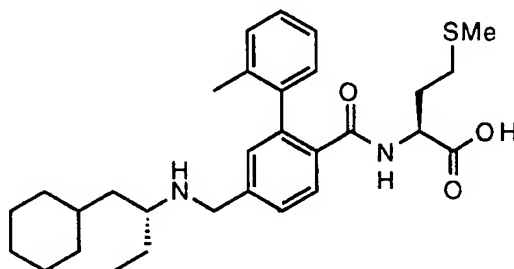
8125



Example 613

N-[4-(3-cyclohexylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

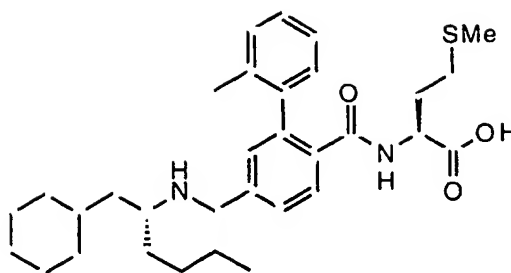
The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺ 497; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.63 (m, 1H), 7.52-7.43 (m, 2H), 7.25-7.04 (m, 4H), 4.06 (m, 1H), 3.97 (d, J=14 Hz, 1H), 3.89 (d, J=14 Hz, 1H), 2.85 (m, 1H), 2.17-1.94 (m, 5H), 1.94 (s, 3H), 1.84-1.52 (m, 7H), 1.50-1.02 (m, 9H), 0.90-0.77 (m, 2H); Anal. Calcd for C₂₉H₄₀N₂O₃S•1.55 H₂O: C, 66.39; H, 8.28; N, 5.34. Found: 66.39; H, 7.89; N, 5.11.



Example 614

N-[4-(4-cyclohexylbutan-3-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺ 511; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.48 (d, J=8 Hz, 1H), 7.36 (d, J=6 Hz, 1H), 7.25-7.09 (m, 4H), 7.00-6.85 (m, 1H), 3.80-3.65 (m, 3H), 2.42 (m, 1H), 2.20-1.50 (m, 15H), 1.41-1.06 (m, 8H), 0.90-0.70 (m, 2H), 0.79 (t, J=7 Hz, 3H); Anal. Calcd for C₃₀H₄₁LiN₂O₃S•1.25 H₂O: C, 66.83; H, 8.13; N, 5.20. Found: 66.86; H, 7.91; N, 4.93.

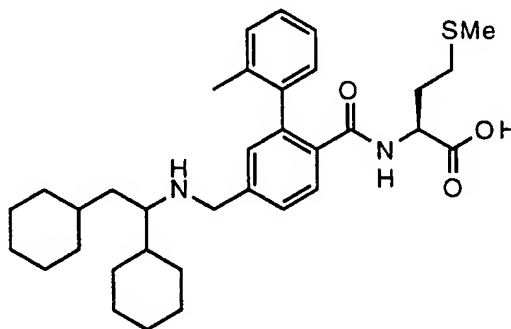
Example 615

N-[4-(6-cyclohexylhexan-5-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium

Salt

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M-H)⁻ 537; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.47 (d, J=8 Hz, 1H), 7.36 (dd, J=8, 1 Hz, 1H), 7.24-7.07 (m, 4H), 6.90 (m, 1H), 3.75-3.62 (m, 3H), 2.45 (m, 1H), 2.18-1.50 (m, 15H), 1.40-1.07 (m, 12H), 0.88-0.75 (m, 5H); Anal. Calcd for

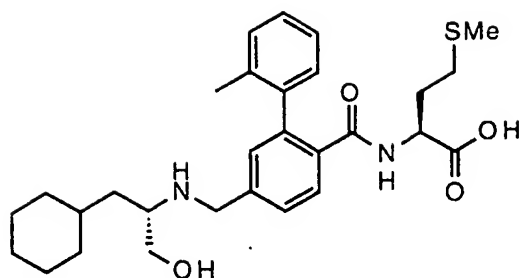
C₃₂H₄₅LiN₂O₃S•1.05 H₂O: C, 68.19; H, 8.42; N, 4.97. Found: 68.19; H, 8.25; N, 4.77.

Example 616

N-[4-(1,2-dicyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium

Salt

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺ 565; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.47 (d, J=8 Hz, 1H), 7.36 (m, 1H), 7.23-7.12 (m, 4H), 6.91 (m, 1H), 3.77-3.63 (m, 3H), 2.30 (m, 1H), 2.15 (m, 1H), 2.03-1.85 (m, 6H), 1.80-1.40 (m, 12H), 1.30-0.65 (m, 15H); Anal. Calcd for C₃₄H₄₇LiN₂O₃S•2.25 MeOH: C, 67.05; H, 8.15; N, 4.60. Found: 67.37; H, 7.69; N, 4.46.



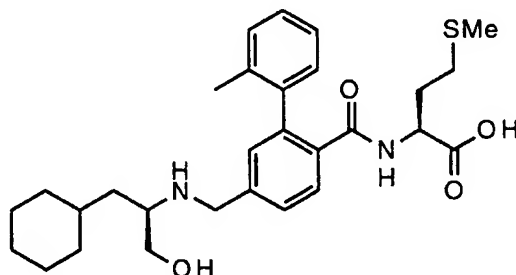
8175

Example 617N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺ 513; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.85 (m, 1H), 7.49 (d, J=7 Hz, 1H), 7.42 (d, J=7 Hz, 1H), 7.23-7.05 (m, 4H), 4.18-4.12 (m, 2H), 3.92-3.84 (m, 2H), 3.45 (m, 1H), 2.65 (m, 1H), 2.18-2.00 (m, 4H), 1.85-1.55 (m, 6H), 1.38-1.08 (m, 10 H), 0.89-0.77 (m, 3H); Anal. Calcd for C₂₉H₄₀N₂O₄S•1.65 H₂O: C, 64.21; H, 8.05; N, 5.16. Found: 64.26; H, 7.64; N, 4.77.

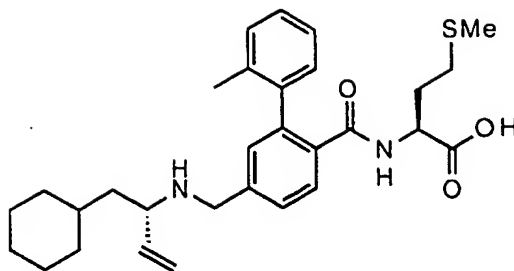
8180

8185

Example 618N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionineTrifluoroacetate Salt

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺ 513; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.85 (m, 1H), 7.49 (d, J=7 Hz, 1H), 7.42 (d, J=7 Hz, 1H), 7.23-7.05 (m, 4H), 4.18-4.12 (m, 2H), 3.92-3.84 (m, 2H), 3.45 (m, 1H), 2.65 (m, 1H), 2.18-2.00 (m, 4H), 1.85-1.55 (m, 6H), 1.38-1.08 (m, 10 H), 0.89-0.77 (m, 3H); Anal. Calcd for C₂₉H₄₀N₂O₄S•C₂HF₃O₂•1.70 H₂O: C, 56.64; H, 6.81; N, 4.26. Found: 56.67; H, 6.89; N, 4.11.

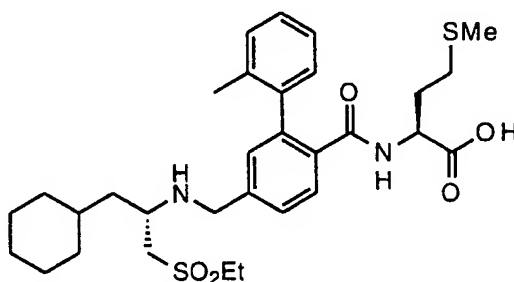
8195

**Example 619**

8200 N-[4-(2-cyclohexylprop-1-en-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine
Lithium Salt

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M-H)⁻ 507; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.47 (d, J=8 Hz, 1H), 7.32 (m, 1H), 7.25-7.07 (m, 4H), 6.93 (m, 1H), 5.52 (ddd, J=17, 10, 8 Hz, 1H), 5.05 (dd, J=10, 2 Hz, 1H), 4.97 (dd, J=17, 2 Hz, 1H), 3.77 (d, J=15 Hz, 1H), 3.70 (m, 1H), 3.57 (d, J=15 Hz, 1H), 2.94 (m, 1H), 2.17-1.50 (m, 15H), 1.38-1.06 (m, 6H), 0.90-0.77 (m, 2H); Anal. Calcd for C₃₀H₃₉LiN₂O₃S•1.90 H₂O: C, 65.65; H, 7.86; N, 5.10. Found: 65.64; H, 7.34; N, 4.80.

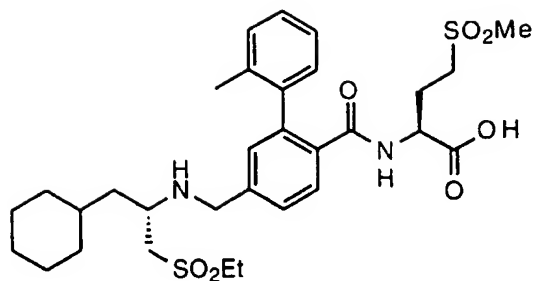
8210

**Example 620**

N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

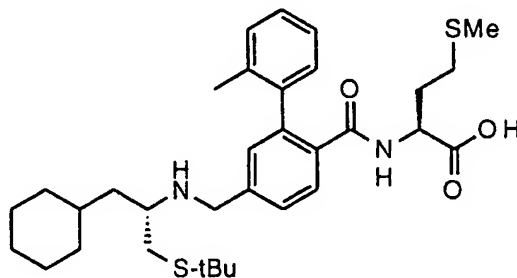
8215 The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺ 589; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.52 (d, J=8 Hz, 1H), 7.38 (dd, J=8, 1 Hz, 1H), 7.27-7.10 (m, 4H), 6.97 (m, 1H), 3.83-3.68 (m, 3H), 3.33 (m, 1H), 3.20-3.07 (m, 3H), 2.97 (dd, J=14, 5 Hz, 1H), 2.28-1.81 (m, 8H), 1.78-1.08 (m, 16H), 0.92-0.75 (m, 2H); Anal. Calcd for C₃₁H₄₃LiN₂O₅S₂•4.25 H₂O: C, 55.46; H, 7.73; N, 4.17. Found: 55.43; H, 6.94; N, 4.03.

8220

Example 621

8225 N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methanesulfonylbutanoic acid Lithium Salt

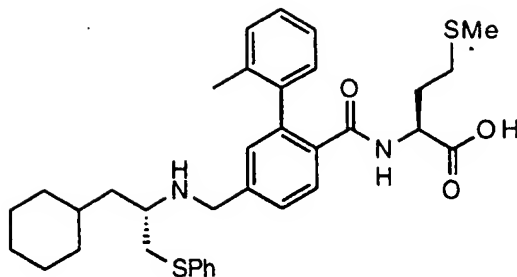
The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M-H)⁻619; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.53 (d, J=8 Hz, 1H), 7.37 (d, J=8 Hz, 1H), 7.25-7.09 (m, 4H), 6.97 (m, 1H), 3.78-3.65 (m, 3H), 3.25 (m, 1H),
 8230 3.21-2.91 (m, 4H), 2.80 (s, 3H), 2.28-1.07 (m, 21H), 0.92-0.84 (m, 2H); Anal. Calcd for C₃₁H₄₃LiN₂O₇S₂•1.25 H₂O: C, 57.35; H, 7.06; N, 4.31. Found: 57.35; H, 7.03; N, 4.11.

Example 622

8235 N-[4-(3-cyclohexyl-1-t-butylthiopropyl-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

The desired compound was prepared according to the method of Example 158 MS (CI/NH₃) m/z: (M+H)⁺584; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.747 (d, J=8 Hz, 1H), 7.37 (dd, J=8, 1 Hz, 1H), 7.23-7.13 (m, 4H), 6.97 (m, 1H), 3.87-3.72 (m, 2H), 3.65 (m, 1H), 2.63 (m, 1H), 2.18-1.77 (m, 8H), 1.74-1.00 (m, 24 H), 0.91-0.68 (m, 2H); Anal. Calcd for C₃₃H₄₇LiN₂O₃S₂•4.50 EtOH: C, 59.39; H, 7.78; N, 4.70. Found: 59.65; H, 7.43; N, 3.91.

8245

Example 623N-[4-(3-cyclohexyl-1-phenylthiopropyl)-2-aminomethyl]-2-(2-methylphenyl)benzoyl-L-methionine Lithium Salt


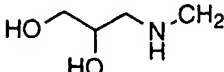
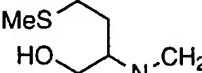
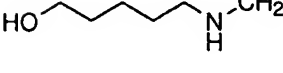
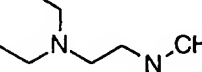
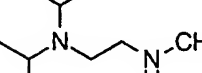
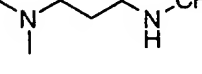
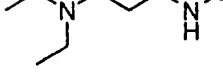
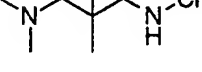
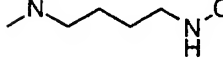
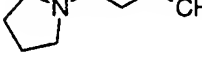
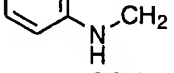
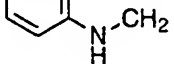
The desired compound was prepared according to the method of Example 158 MS (Cl/NH₃) m/z: (M+H)⁺605; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.7.46 (d, J=8 Hz, 1H), 7.34-6.85 (m, 11H), 3.86-3.65 (m, 3H), 3.11 (dd, J=13, 5 Hz, 1H), 2.87 (m, 1H), 2.67 (m, 1H), 2.17-0.60 (m, 23H); Anal. Calcd for C₃₅H₄₃LiN₂O₃S₂•1.20 H₂O: C, 66.47; H, 7.24; N, 4.43. Found: 66.43; H, 7.27; N, 4.49.

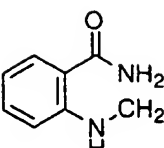
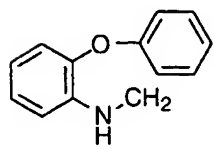
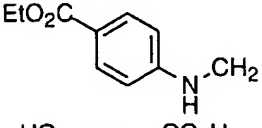
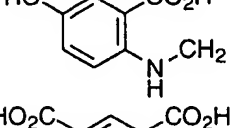
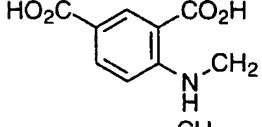
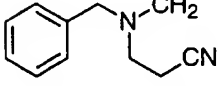
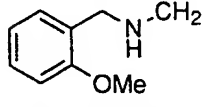
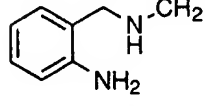
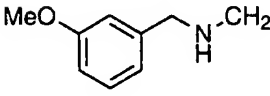
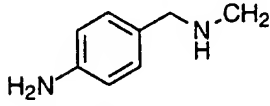
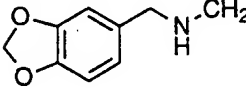
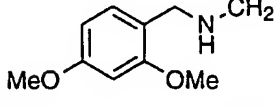
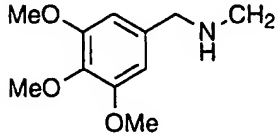
Examples 626-668 and Examples 669-758

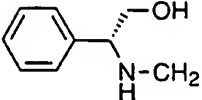
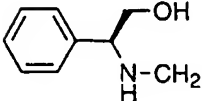
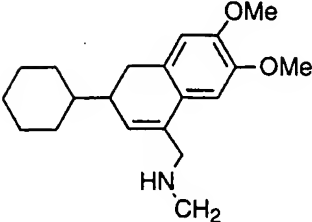
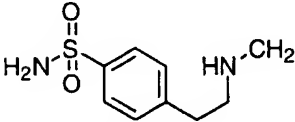
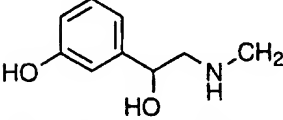
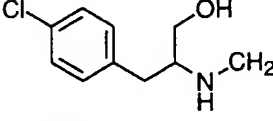
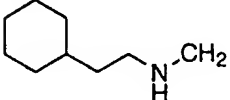
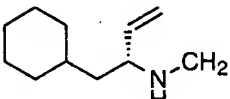
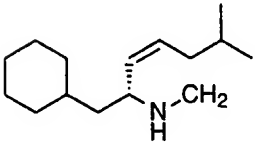
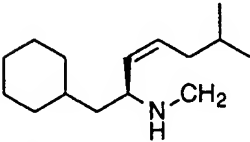
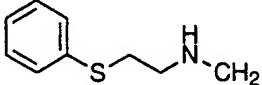
Compounds 626-667, 669-722, and 723-727 were synthesized by reductive amination of the compound described in Example 625, by the procedure described in Example 158

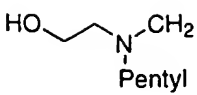
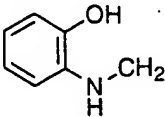
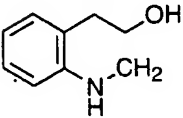
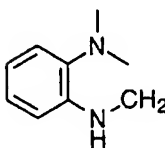
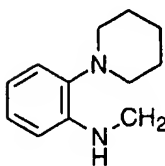
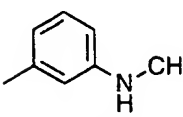
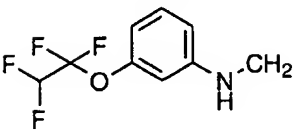
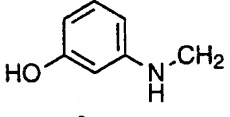
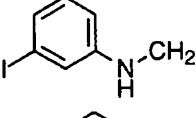
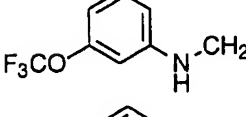
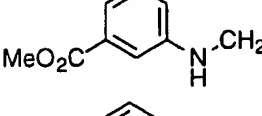
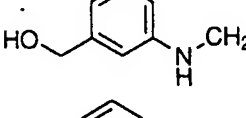
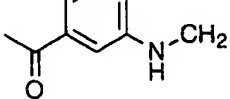
R₁ = Ph

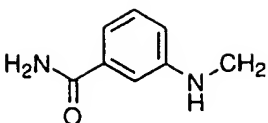
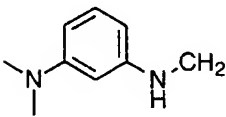
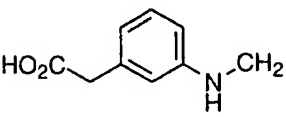
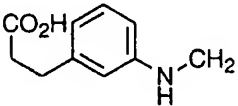
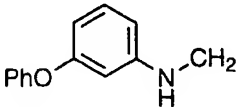
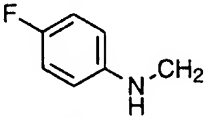
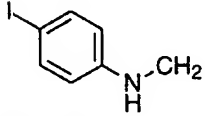
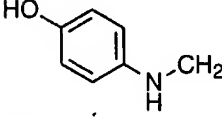
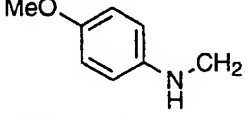
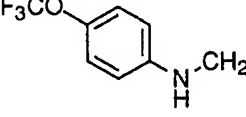
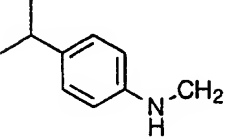
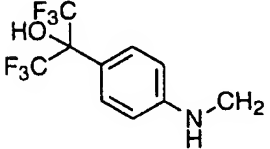
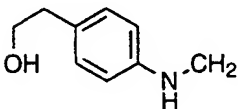
<u>Example</u>	<u>R₃L₁</u>	<u>MS (M+H)⁺</u>
626		419
627		475
628		417
629		431
630		445

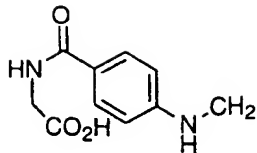
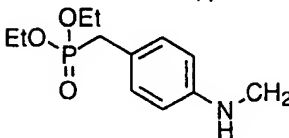
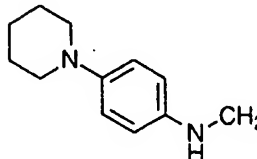
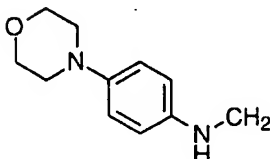
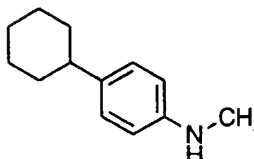
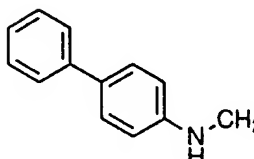
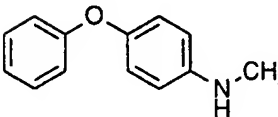
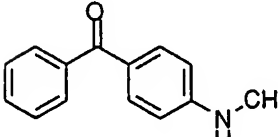
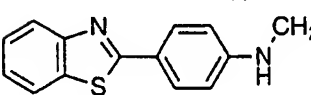
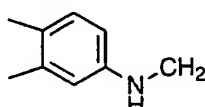
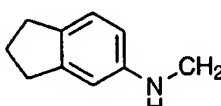
631		417
632		433
633		477
634		445
635		458
636		486
637		444
638		472
639		472
640		458
641		456
642		453
643		479

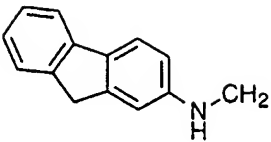
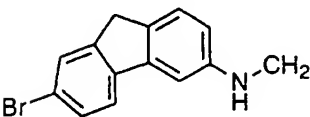
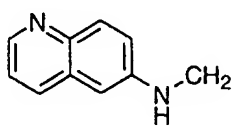
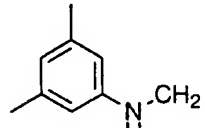
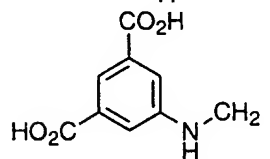
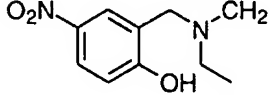
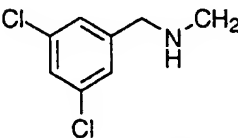
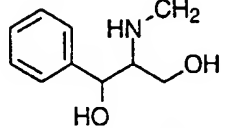
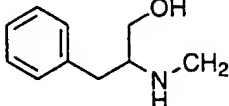
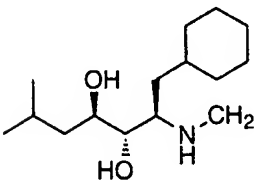
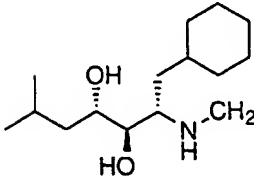
644		478
645		527
646		507
647		495
648		459
649		502
650		479
651		450
652		479
653		464
654		493
655		509
656		539

657		479
658		479
659		643
660		542
661		495
662		527
663		469
664		495
665		551
666		551
667		495

669	 <chem>CCCCCNCCO</chem>	457
670	 <chem>Oc1ccccc1NC</chem>	435
671	 <chem>CC(O)CNc1ccccc1</chem>	479
672	 <chem>CN(C)Cc1ccccc1</chem>	478
673	 <chem>C1CCN(C1)Cc2ccccc2</chem>	518
674	 <chem>Cc1cccc(NC)c1</chem>	449
675	 <chem>COc1ccc(NC)cc1C(F)(F)F</chem>	551
676	 <chem>Oc1cccc(NC)c1</chem>	451
677	 <chem>Ic1cccc(NC)c1</chem>	561
678	 <chem>COc1ccc(NC)cc1C(F)(F)F</chem>	519
679	 <chem>COC(=O)c1ccc(NC)cc1</chem>	493
680	 <chem>OCCc1ccc(NC)cc1</chem>	465
681	 <chem>CC(=O)c1ccc(NC)cc1</chem>	477

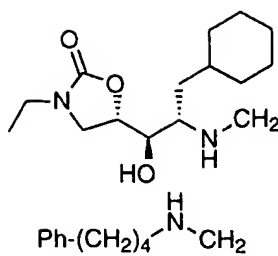
682		478
683		478
684		493
685		507
686		527
687		453
688		561
689		451
690		465
691		519
692		477
693		601
694		479

695	 <chem>NC(=O)C(C(=O)O)CNc1ccc(cc1)</chem>	536
696	 <chem>CCOP(=O)(OCC)CNc1ccc(cc1)</chem>	585
697	 <chem>NC1CCCCC1Nc2ccc(cc2)CN</chem>	518
698	 <chem>NC1CCOCC1Nc2ccc(cc2)CN</chem>	520
699	 <chem>NC1CCCCC1Cc2ccc(cc2)CN</chem>	517
700	 <chem>NC1CCCCC1Cc2ccc(cc2)CN</chem>	511
701	 <chem>NC1CCCCC1Oc2ccc(cc2)CN</chem>	527
702	 <chem>NC(=O)c1ccccc1c2ccc(cc2)CN</chem>	539
703	 <chem>NC1CCCCC1S2=NC3=CC=CC=C3SC2=N1</chem>	568
704	 <chem>CC1=CC=C(C=C1)C2=CC=CC=C2CN</chem>	463
705	 <chem>NC1CCCCC1Cc2ccc(cc2)CN</chem>	475

706	 <chem>NCCc1ccc2c(c1)c3ccccc3cc2</chem>	523
707	 <chem>NCCc1ccc2c(c1)Cc3cc(Br)ccc32</chem>	601
708	 <chem>NCCc1ccc2c(c1)ncn2</chem>	486
709	 <chem>NCCc1cc(C)c(C)cc1</chem>	463
710	 <chem>NCCc1cc(C(=O)O)c(C(=O)O)cc1</chem>	523
711	 <chem>NCCc1cc(OC)c([N+](=O)[O-])cc1</chem>	538
712	 <chem>NCCc1cc(Cl)cc(Cl)c1</chem>	517
713	 <chem>NCC(O)C(O)Cc1ccccc1</chem>	509
714	 <chem>NCC(O)Cc1ccccc1</chem>	493
715	 <chem>NCC(O)C(O)C(C)Cc1ccccc1</chem>	585
716	 <chem>NCC(O)C(O)C(C)Cc1ccccc1</chem>	585

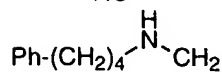
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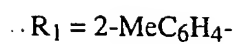
601



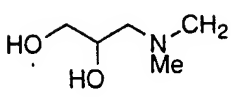
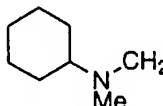
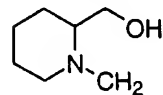
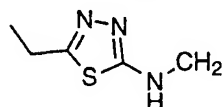
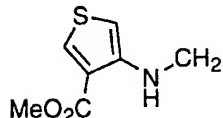
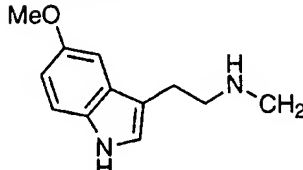
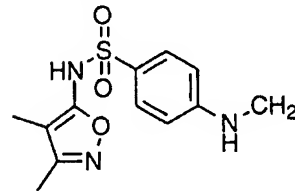
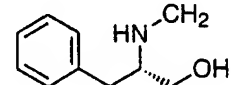
718

491





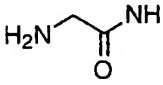
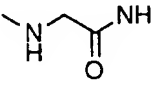
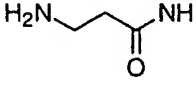
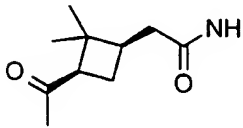
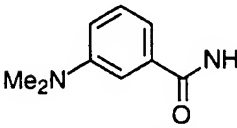
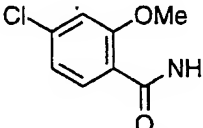
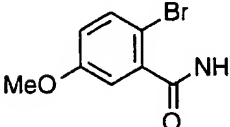
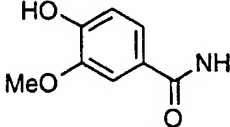
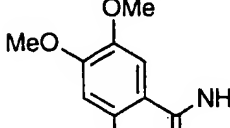
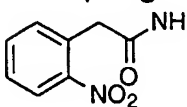
8265

<u>Example</u>	<u>R₃L₁</u>	<u>MS (M+H)⁺</u>
719		461
720		459
721		483
723		485
724		513
725		549
726		623
727		506

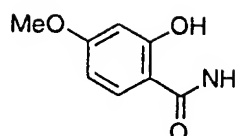
Examples 748-758 were prepared by the procedure described in Example 57

8270

$R_1 = \text{Ph}$

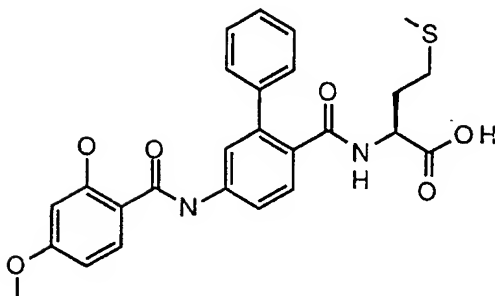
<u>Example</u>	<u>R_3L_1</u>	<u>MS (M+H)⁺</u>
748		402
749		416
750		416
751		511
752		492
753		513
754		558
755		489
756		635
757		508

758



489

8275

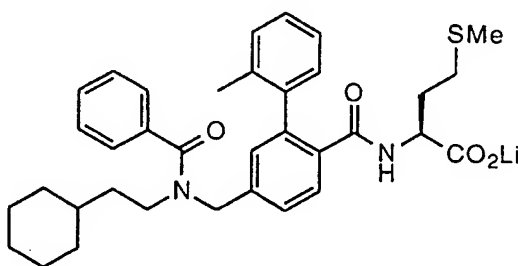
Example 759

(2S)-2-N-[4-(N-benzyl)-N-3-pyridylaminomethyl]-2-(2-methylphenyl)benzoylamino-4-methanesulfonylbutanoic acid.

8280

The desired compound was prepared according to the method of Example 157. ^1H (300 MHz., DMSO d_6): δ 12.8, (1H, s), 8.18, (1H, d $J=8\text{Hz}$), 7.50 (2H, d, $J=8\text{Hz}$), 7.38 - 7.09 (14H, m), 4.83 (2H, s), 4.78 (2H, s), 4.21 (1H, s), 2.91 (3H, s), 2.76 (1H, m), 2.02, (1H, m), 2.00, (3H, s), 1.85 (2H, m). MS (DCI - NH_3) m/z 572 (MH^+); Anal calcd for $\text{C}_{32}\text{H}_{33}\text{N}_3\text{O}_5 \cdot \text{H}_2\text{O}$: C, 65.18. H, 5.98. N, 7.13 Found: C, 65.54; H, 5.73; N, 6.82.

8285



8290

Example 762

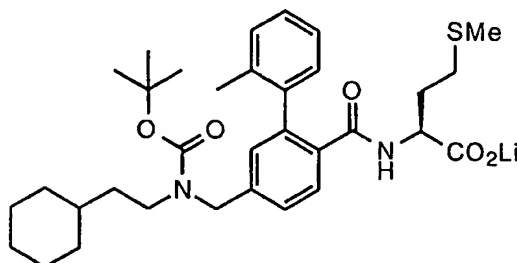
N-[4-N-Benzoyl-N-2-cyclohexylethylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

8295

The desired compound was prepared according to the method of Example 607. The resultant amine was reacted with benzoyl chloride - lithium carbonate under Schotten-Baumann conditions. MS (CI/ NH_3) m/z : (M-H^-) 585; ^1H NMR (DMSO- d_6 , 300 MHz) δ 7.53 (m, 1H), 7.45-7.32 (m, 6H), 7.25-7.08 (m, 4H), 6.94 (m, 1H), 4.73-4.68 (m, 2H),

3.67-3.61 (m, 1H), 3.18-3.10 (m, 2H), 2.17-1.94 (m, 7H), 1.70-1.15 (m, 14H), 0.68-0.55 (m, 2H); Anal. Calcd for $C_{35}H_{41}LiN_2O_4S \cdot 1.80 H_2O$: C, 67.25; H, 7.19; N, 4.48. Found: C, 67.23; H, 6.78; N, 4.28.

8300



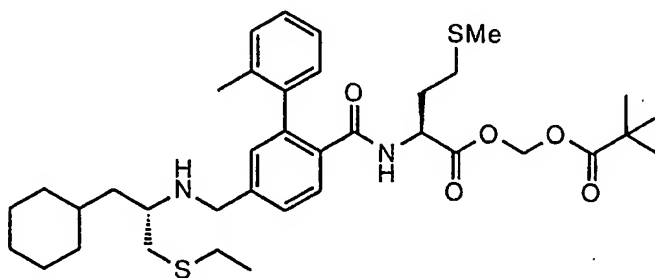
Example 763

N-[4-N-t-Butyloxycarbonyl-N-2-cyclohexylethylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

8305

The desired compound was prepared according to the method of Example 607. The resultant amine was reacted with di-t-butyl dicarbonate under Schotten-Baumann conditions. MS (CI/ NH_3) m/z: (M-H)⁻ 581; 1H NMR (DMSO- d_6 , 300 MHz) δ 7.51 (m, 1H), 7.31-6.93 (m, 6H), 4.41 (s, 2H), 3.69-3.61 (m, 1H), 3.25-3.13 (m, 2H), 2.14 (m, 1H), 2.02-1.91 (m, 2H), 1.91 (s, 3H), 1.66-1.51 (m, 8H), 1.45-1.05 (m, 16H), 0.88-0.75 (m, 2H); Anal. Calcd for $C_{23}H_{45}LiN_2O_5S \cdot 1.70 H_2O$: C, 64.00; H, 7.88; N, 4.52. Found: C, 63.99; H, 7.49; N, 4.33.

8310



8315

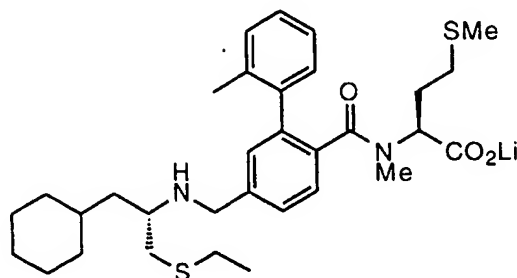
Example 764

Pivaloyloxymethyl N-[4-N-(3-Cyclohexyl-1-ethylthiopropyl)-N-methylaminomethyl-2-(2-methylphenyl)benzoyl]methionine hydrochloride salt

The desired compound was prepared by reaction of the compound resulting from Example 763 under conditions described in Example 500, followed by treatment with 4N HCl - dioxane. MS (CI/ NH_3) m/z: (M+H)⁺ 671; 1H NMR (DMSO- d_6 , 300 MHz) δ 8.42 (d, J=7.5 Hz, 1H), 7.65 (d, J=8.1 Hz, 1H), 7.55 (d, J=7.5 Hz, 1H), 7.49-7.42 (m, 1H),

8320

7.26-7.06 (m, 3H), 5.73 (d, J=5.8 Hz, 1H), 5.65 (d, J=5.8 Hz, 1H), 4.29 (brs, 2H), 3.25-3.17 (m, 1H), 3.04-2.97 (m, 1H), 2.86-2.77 (m, 1H), 2.24-2.02 (m, 6H), 1.94 (s, 3H),
 8325 1.83-1.40 (m, 12H), 1.25-1.07 (m, 6H), 1.13 (s, 9H), 0.93-0.77 (m, 2H); Anal. Calcd for $C_{37}H_{55}ClN_2O_5S_2$: C, 62.82; H, 7.84; N, 3.96. Found: C, 62.71; H, 8.03; N, 3.90.



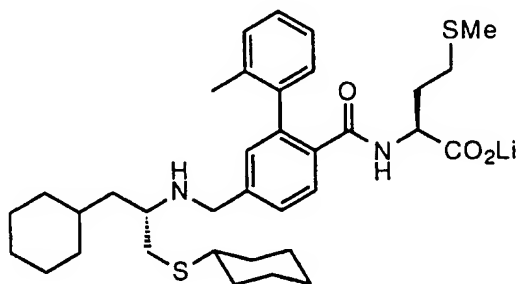
8330

Example 765

N-[4-*N*-(3-Cyclohexyl-1-ethylthiopropyl)-*N*-methylaminomethyl]-2-(2-methylphenyl)benzoyl]-*N*-methylmethionine lithium salt

The desired compound was prepared according to the method of Example 158. MS (Cl/NH₃) *m/z*: (M-H)⁻ 569; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.38 (d, J=7.8 Hz, 1H),
 8335 7.24-7.04 (m, 6H), 4.53-4.45 (m, 1H), 3.85-3.67 (m, 2H), 2.67-2.59 (m, 2H), 2.50-2.38 (m, 5H), 2.18-1.92 (m, 5H), 1.87 (s, 3H), 1.70-1.05 (m, 17H), 0.93-0.72 (m, 2H); Anal. Calcd for $C_{32}H_{45}LiN_2O_3S_2 \cdot 1.20 H_2O$: C, 64.23; H, 7.98; N, 4.68. Found: C, 64.27; H, 7.97; N, 4.66.

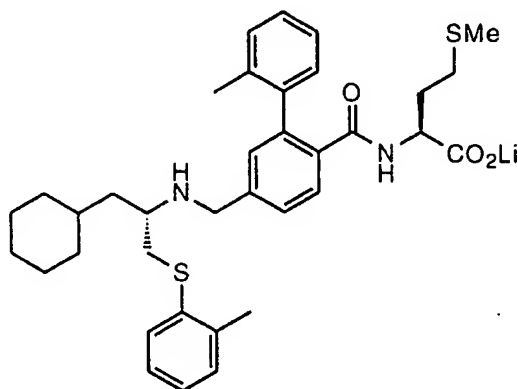
8340

Example 766

N-[4-*N*-(3-Cyclohexyl-1-cyclohexylthiopropyl)-*N*-methylaminomethyl]-2-(2-methylphenyl)benzoyl]-*N*-methylmethionine lithium salt

The desired compound was prepared according to the method of Example 158. MS (Cl/NH₃) *m/z*: (M-H)⁻ 609; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.48 (d, J=7.7 Hz, 1H),
 8345 7.34 (m, 1H), 7.21-7.06 (m, 4H), 6.96-6.88 (m, 1H), 3.83-3.66 (m, 3H), 2.64-2.54 (m,

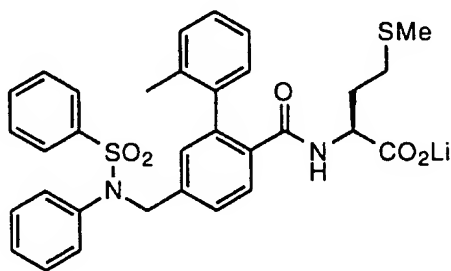
2H), 2.15-1.90 (m, 4H), 1.90 (s, 3H), 1.87-1.02 (m, 26H), 0.87-0.75 (m, 2H); Anal.
 Calcd for $C_{35}H_{49}LiN_2O_3S_2 \cdot 1.05 H_2O \cdot 1.60 TFA$: C, 56.08; H, 6.49; N, 3.42. Found: C,
 8350 56.05; H, 6.50; N, 3.49.



Example 767

8355 *N*-[4-*N*-(3-Cyclohexyl-1-(2-methylphenyl)thiopropyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158. MS (CI/NH₃) *m/z*: (M-H)⁻ 617; ¹H NMR (DMSO-d₆, 300 MHz) δ 7.45 (d, *J*=7.8 Hz, 1H), 7.32-6.85 (m, 10H), 3.82-3.64 (m, 3H), 3.06 (dd, *J*=12.5, 4.4 Hz, 1H), 2.88-2.78 (m, 1H), 2.74-2.62 (m, 1H), 2.23 (s, 3H), 2.16-2.08 (m, 2H), 1.97-1.90 (m, 2H), 1.92 (s, 3H), 1.85-0.98 (m, 14H), 0.90-0.63 (m, 2H); Anal. Calcd for $C_{36}H_{45}LiN_2O_3S_2 \cdot 1.0 H_2O$: C, 67.16; H, 7.51; N, 4.35. Found: C, 67.17; H, 7.30; N, 4.24.



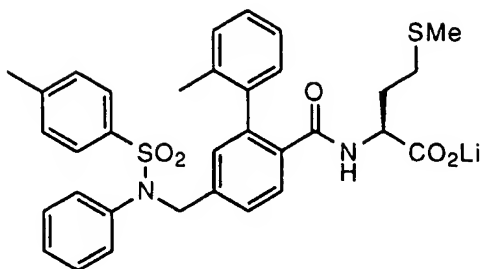
8365

Example 769

N-[4-*N*-(*N*-phenyl-*N*-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157.
 8370 ¹H(CD₃OD): δ 7.6-7.7 (2H, m); 7.5-7.6 (2H, m); 7.3-7.4 (1H, m); 7.3-7.1 (10H, m);

6.9-7.1 (2H, m); 4.9 (2H, s); 4.1-4.3 (1H, m); 2.1-1.5 (10H, m). ESI(-)/MS: 587(M-Li); 407.



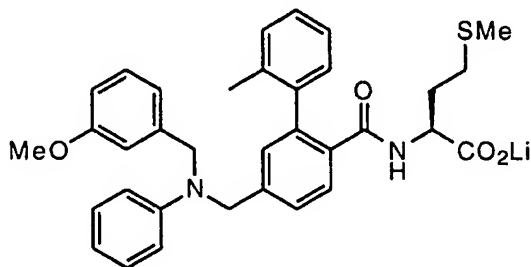
8375

Example 770

N-[4-N-(N-phenyl-N-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157.

8380 $^1\text{H}(\text{CD}_3\text{OD})$: δ 7.6-7.7 (2H, m); 7.5-7.6 (2H, m); 7.3-7.4 (1H, m); 7.3-7.1 (10H, m); 6.9-7.1 (2H, m); 4.9 (2H, s); 4.1-4.3 (1H, m); 2.4 (3H, m); 1.5-2.1 (10H, m). ESI(-)/MS: 601(M-Li); 421



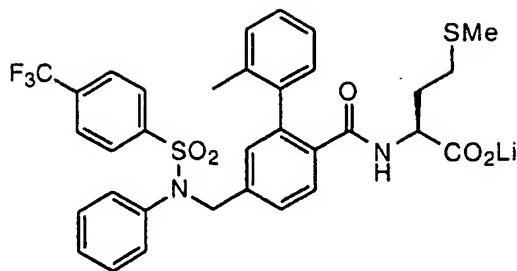
8385

Example 779

N-[4-N-(N-phenyl-N-(3-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157.

8390 $^1\text{H}(\text{MeOH-d}_4)$: δ 7.6-7.7 (1H, d); 7.3-7.4 (1H, d); 7.0-7.3 (8H, m); 6.6-6.85 (6H, m); 4.7 (2H, s); 4.65 (2H, s); 4.18-4.3 (1H, m); 3.65 (3H, s); 1.5-2.2 (10H, m). ESI(-)/MS: 567(M-Li); 447; 366; 281.



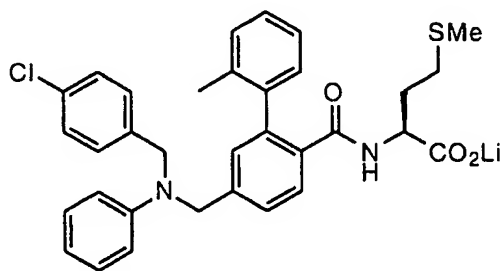
8395

Example 780

N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157.

8400 $^1\text{H}(\text{MeOH-}d_4)$: δ 7.8-7.95 (4H, m); 7.5-7.6 (1H, d), 7.3-7.4 (1H, d); 7.1-7.3 (7H, m); 6.95-7.1 (3H, m); 4.9 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m); 1.5-1.7 (1H, m). ESI(-)/MS: 655(M-Li); 475, 431.



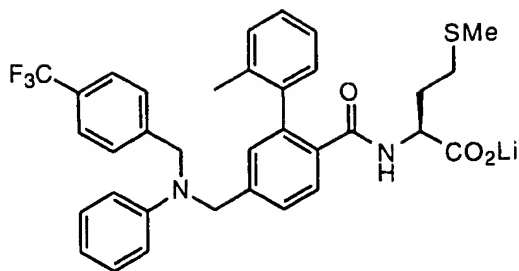
8405

Example 781

N-[4-N-(N-phenyl-N-(4-chlorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157.

8410 $^1\text{H}(\text{MeOH-}d_4)$: δ 7.6-7.7 (1H, d); 7.3-7.4 (1H, d); 7.18-7.30 (6H, m); 7.0-7.2 (4H, m); 6.6-6.78 (4H, m); 4.71 (2H, s); 4.64 (2H, s); 4.2-4.3 (1H, m); 1.55-2.2 (10H, m). ESI(-)/MS: 571(M-Li); 367, 255.



8415

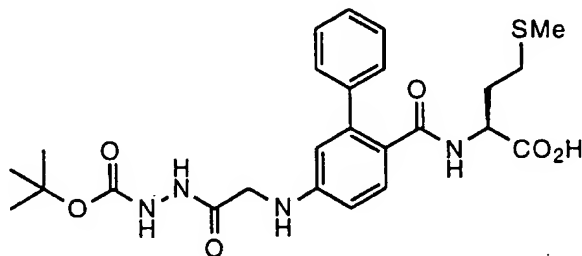
Example 782

N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157.

8420 $^1\text{H}(\text{MeOH}-d_4)$: δ 7.55-7.7 (3H, m); 7.3-7.5 (3H, m); 7.2-7.3 (3H, m); 7.0-7.18 (4H, m); 4.8 (4H, d); 4.18-4.3 (1H, m); 1.6-2.2 (10H, m).

ESI(-)/MS: 605(M-Li); 367; 283.



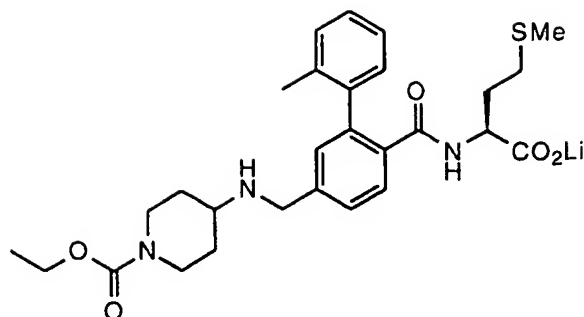
8425

Example 784

N-[4-N(t-Butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine

The desired compound was prepared according to the method of Example 57, except *t*-Butylcarbazatocarbonylmethyl bromide was used as the alkylating agent. ^1H nmr (300

8430 MHz, DMSO- d_6): δ 9.79 (s, 1 H), 8.85 (s, 1 H), 8.12 (d, 1 H), 7.47-7.29 (m, 6 H), 6.65 (br d, 1 H), 6.56 (d, 1 H), 6.43 (t, 1 H), 4.30 (m, 1 H), 3.81 (d, 2 H), 2.32 (m, 2 H), 2.05 (br s, 6 H), 1.90 (m, 2 H), 1.47 (s, 9 H). MS (APCI +) m/e 517 (M+H) $^+$.

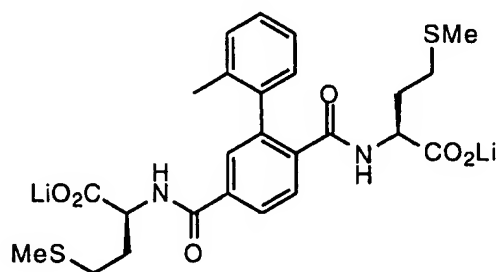


8435

Example 806*N*-[4-(1-ethoxycarbonylpiperidin-4-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

8440

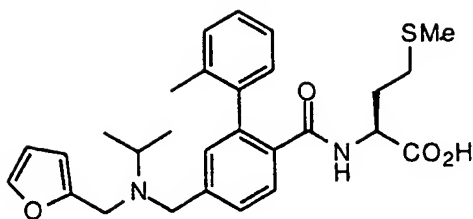
The desired compound was prepared according to the method of Example 158. ¹H nmr (300 MHz, DMSO-d₆): δ 7.48 (d, 1 H), 7.38 (dd, 1 H), 7.26-7.10 (m, 5 H), 6.90 (m, 1 H), 4.00 (q, 2 H), 3.88-3.73 (m, 4 H), 3.66 (m, 1 H), 2.85 (m, 2 H), 2.56 (m, 1 H), 2.18 (m, 2 H), 2.00 (m, 5 H), 1.92 (br s, 3 H), 1.80 (m, 1 H), 1.76 (m, 1 H), 1.68 (m, 1 H), 1.58 (m, 1 H), 1.16 (t, 3 H). MS (ESI⁻): m/e 526 (M-H)⁻.



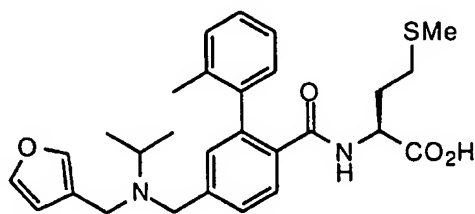
8445

Example 830*N*-[4-(*N*-[3-methylthio-1-carboxyprop-2-yl]aminocarbonyl)-2-phenylbenzoyl]methionine

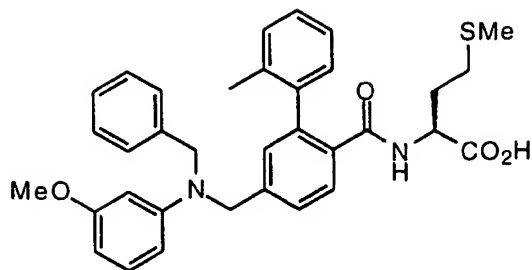
The desired compound was prepared according to the method of Example 451. ¹H NMR (d₆-DMSO): δ 1.64-1.91 (comp, 2 H), 1.93 (s, 3 H), 1.98-2.22 (comp, 10 H), 2.46-2.62 (comp, 2 H), 4.18-4.28 (m, 1 H), 4.49-4.58 (m, 1 H), 7.14-7.26 (comp, 4 H), 7.58 (d, *J* = 7.8 Hz, 1 H), 7.74-7.79 (br s, 1 H), 7.96 (dd, *J* = 1.7, 7.8 Hz, 1 H), 8.24-8.32 (br, 1 H), 8.74 (d, *J* = 7.4 Hz, 1 H), 12.50-12.93 (br, 2 H). LRMS (ESI⁻): 517 (M-1)⁻.

**Example 831****N-[4-N-(furan-2-ylmethyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Example 158. ¹H NMR (d₆-DMSO): δ 1.00 (d, J= 6.6 Hz, 6 H), 1.50-1.63 (m, 1 H), 1.63-1.76 (m, 1 H), 1.77-2.18 (comp, 8 H), 2.89 (sept, J= 6.6 Hz, 1 H), 3.56 (s, 2 H), 3.63 (s, 2 H), 3.66-3.80 (br, 1 H), 6.23 (d, J= 2.9 Hz, 1 H), 6.35 (dd, J= 1.8, 3.3 Hz, 1 H), 6.93 (d, J= 6.2 Hz, 1 H), 7.10-7.26 (br comp, 4 H), 7.37 (d, J= 8.1 Hz, 1 H), 7.48 (d, J= 7.7 Hz, 1 H), 7.53 (dd, J= 0.7, 1.8 Hz, 1 H). LRMS (ESI⁻): 493 (M-1)⁻.

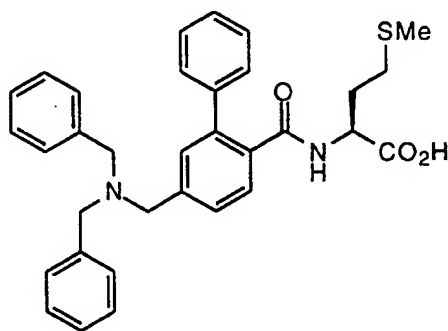
**Example 832****N-[4-N-(furan-3-ylmethyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Example 158. ¹H NMR (d₆-DMSO): δ 1.00 (d, J= 6.6 Hz, 6 H), 1.49-1.76 (comp, 2 H), 1.76-2.19 (comp, 8 H), 2.88 (sept, J= 6.6 Hz, 1 H), 3.37 (s, 2 H), 3.57 (s, 2 H), 3.68-3.78 (br, 21 H), 6.36 (s, 1 H), 6.93 (d, J= 6.2 Hz, 1 H), 7.08-7.26 (comp, 4 H), 7.39 (d, J= 8.1 Hz, 1 H), 7.48 (d, J= 7.6 Hz, 1 H), 7.52-7.57 (comp, 2 H). LRMS (ESI⁻): 493 (M-1)⁻.

**Example 833**

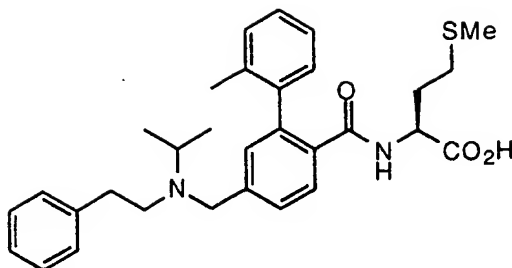
8480 *N*-[4-*N*-benzyl-*N*-3-methoxyphenylaminomethyl-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-2.10 (comp, 10 H), 3.60 (s, 3 H), 3.64-3.74 (br, 1 H), 4.69 (s, 2 H), 4.75 (s, 2 H), 6.15-6.18 (br comp, 2 H), 6.20 (d, *J* = 1.9 Hz, 1 H), 6.29 (dd, *J* = 2.3, 9.2 Hz, 1 H), 6.90-7.03 (comp, 3 H), 7.08-7.34 (comp, 9 H), 7.50 (d, *J* = 7.7 Hz, 1 H). LRMS (ESI⁻): 467 (M-1)⁻.

**Example 834**

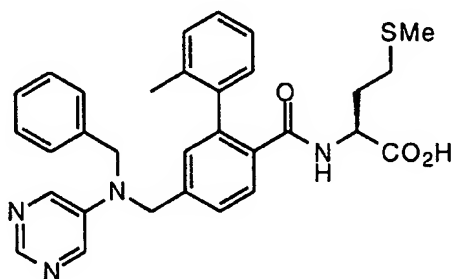
8490 *N*-[4-*N,N*-dibenzylaminomethyl-2-phenylbenzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (d₆-DMSO): δ 1.74-1.95 (comp, 2 H), 1.99 (s, 3 H), 2.15-2.34 (comp, 2 H), 4.17-4.37 (comp, 6 H), 7.21-7.55 (comp, 14 H), 7.60-7.75 (comp, 4 H), 8.57 (d, *J* = 7.8 Hz, 1 H). LRMS (CI⁺): 539 (M+1)⁺.

Example 835

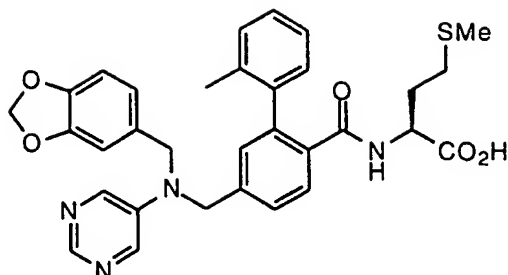
8500 *N*-[4-*N*-(2-phenylethyl)-*N*-isopropylaminomethyl-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (d₆-DMSO): δ 0.94 (d, *J*= 6.3 Hz, 6 H), 1.50-1.77 (comp, 2 H), 1.77-2.20 (comp, 8 H), 2.56-2.66 (comp, 4 H), 2.92 (sept, *J*= 6.3 Hz, 1 H), 3.66 (s, 2 H), 3.70-3.81 (br, 1 H), 6.94 (d, *J*= 5.9 Hz, 1 H), 7.07-7.26 (comp, 9 H), 7.32 (d, *J*= 7.7 Hz, 1 H), 7.46 (dd, *J*= 1.8, 7.7 Hz, 1 H). LRMS (ESI⁻): 517 (M-1)⁻.

Example 836

8510 *N*-[4-*N*-benzyl-*N*-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.74 (br comp, 2 H), 1.86-2.08 (br comp, 8 H), 3.62-3.74 (br, 1 H), 4.83 (s, 2 H), 4.89 (s, 2 H), 6.92-7.03 (br, 1 H), 7.04-7.38 (comp, 11 H), 7.52 (d, *J*= 8.1 Hz, 1 H), 8.22 (s, 2 H), 8.42 (s, 1 H). LRMS (ESI⁻): 539 (M-1)⁻.

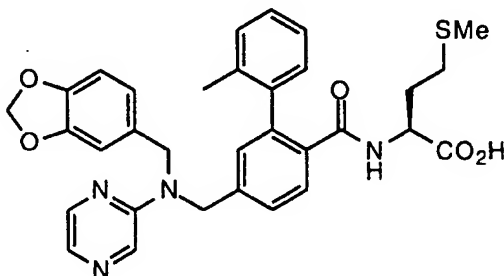


8520

Example 837*N*-[4-*N*-(1,3-benzodiox-5-yl)-*N*-pyrimidin-5-ylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

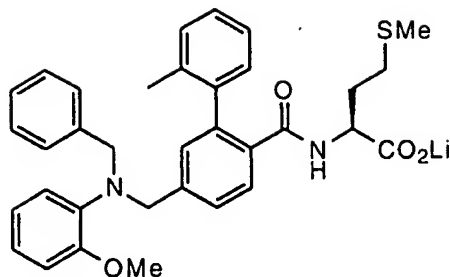
The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.46-1.76 (br comp, 2 H), 1.84-2.05 (br comp, 8 H), 3.56-3.67 (br, 1 H), 4.71 (s, 2 H), 4.86 (s, 2 H), 6.77 (dd, *J* = 1.6, 7.8 Hz, 1 H), 6.83-6.88 (comp, 2 H), 6.90-6.98 (br comp, 2 H), 7.0 (s, 1 H), 7.07-7.24 (br comp, 3 H), 7.33 (dd, *J* = 1.9, 8.1 Hz, 1 H), 7.51 (d, *J* = 7.7 Hz, 1 H), 8.23 (s, 2 H), 8.42 (s, 1 H). LRMS (ESI⁻): 583 (M⁻1)⁻.

8530

Example 838*N*-[4-*N*-(1,3-benzodiox-5-yl)-*N*-pyridizin-2-ylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

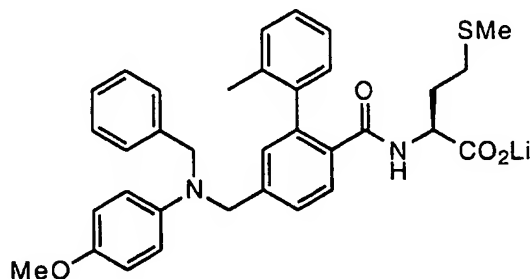
The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.49-1.72 (comp, 2 H), 1.88-2.06 (comp, 8 H), 3.60-3.71 (br, 1 H), 4.75-4.80 (br, 2 H), 4.90 (s, 2 H), 5.96 (s, 2 H), 6.75 (dd, *J* = 1.7, 7.8 Hz, 1 H), 6.80-6.83 (comp, 2 H), 6.90-6.96 (comp, 3 H), 7.05-7.22 (br, 3 H), 7.29 (dd, *J* = 1.7, 8.2 Hz, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.80 (d, *J* = 2.4 Hz, 1 H), 8.03-8.09 (comp, 2 H).

8540

Example 839

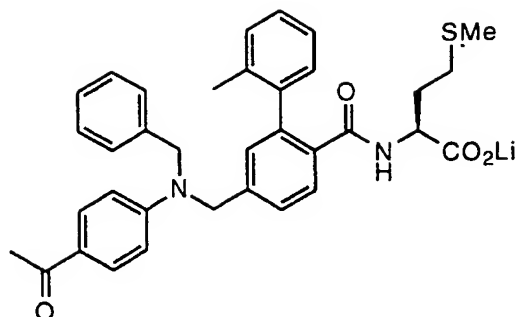
N-[4-(N-benzyl-N-(2-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.47-1.75 (comp, 2 H), 1.76-2.05 (comp, 8 H), 3.66-3.77 (br, 1 H), 3.83 (s, 3 H), 4.22 (s, 2 H), 4.26 (s, 2 H), 6.68-6.74 (m, 1 H), 6.81-6.98 (comp, 4 H), 7.02-7.08 (br, 1 H), 7.10-7.37 (comp, 9 H), 7.44 (d, J = 7.8 Hz, 1 H).

Example 840

N-[4-(N-benzyl-N-(4-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.49-1.62 (m, 1 H), 1.62-1.75 (m, 1 H), 1.78-2.08 (comp, 8 H), 3.61 (s, 3 H), 3.64-3.76 (br, 1 H), 4.58 (s, 2 H), 4.64 (s, 2 H), 6.62-6.74 (comp, 4 H), 6.89-6.96 (m, 1 H), 7.01 (s, 1 H), 7.08-7.33 (comp, 9 H), 7.47 (d, J = 7.8 Hz, 1 H).

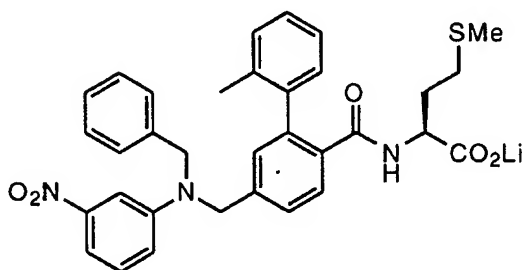
**Example 841**

N-[4-(*N*-benzyl-*N*-(4-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

8565

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.63 (m, 1 H), 1.63-1.75 (m, 1 H), 1.78-2.10 (comp, 8 H), 2.38 (s, 3 H), 3.66-3.76 (br, 1 H), 4.82 (s, 2 H), 4.88 (s, 2 H), 6.74 (d, *J*= 8.8 Hz, 2 H), 6.95 (d, *J*= 6.1 Hz, 1 H), 7.02 (s, 1 H), 7.08-7.36 (comp, 9 H), 7.52 (d, *J*= 8.1 Hz, 1 H), 7.72 (d, *J*= 8.8 Hz, 2 H).

8570

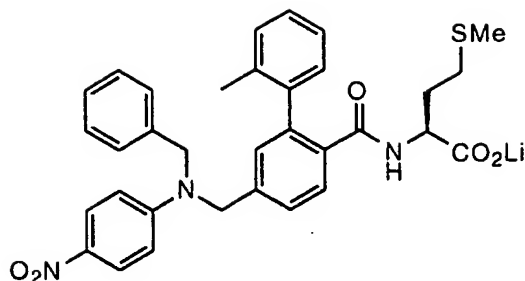
**Example 842**

N-[4-(*N*-benzyl-*N*-(3-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

8575

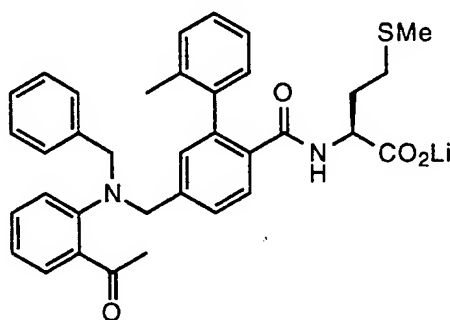
The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.49-1.76 (comp, 2 H), 1.77-2.08 (comp, 8 H), 3.67-3.76 (br, 1 H), 4.85 (s, 2 H), 4.90 (s, 2 H), 6.92-7.01 (br, 1 H), 7.05-7.43 (comp, 14 H), 7.53 (d, *J*= 7.8 Hz, 1 H).

8580

**Example 843**

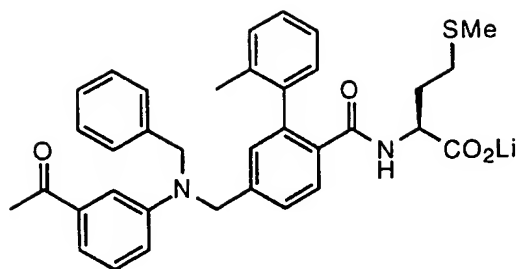
8585 *N*-[4-(*N*-benzyl-*N*-(4-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.62 (m, 1 H), 1.62-1.74 (m, 1 H), 1.76-2.10 (comp, 8 H), 3.64-3.73 (br, 1 H), 4.90 (s, 2 H), 4.95 (s, 2 H), 6.82 (d, *J*= 9.5 Hz, 2 H), 6.94 (d, *J*= 6.1 Hz, 1 H), 7.02 (s, 1 H), 7.08-7.38 (comp, 9 H), 7.53 (d, *J*= 7.8 Hz, 1 H), 8.00 (d, *J*= 9.5 Hz, 2 H).

**Example 844**

8595 *N*-[4-(*N*-benzyl-*N*-(2-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.45-1.70 (br comp, 2 H), 1.86-2.04 (comp, 8 H), 2.60 (s, 3 H), 3.56-3.66 (br, 1 H), 4.21 (app s, 4 H), 6.82-6.94 (br comp, 2 H), 6.99 (t, *J*= 7.4 Hz, 1 H), 7.08 (d, *J*= 7.7 Hz, 1 H), 7.16-7.34 (comp, 10 H), 7.39 (dd, *J*= 1.9, 7.7 Hz, 1 H), 7.45 (d, *J*= 8.0 Hz, 1 H).

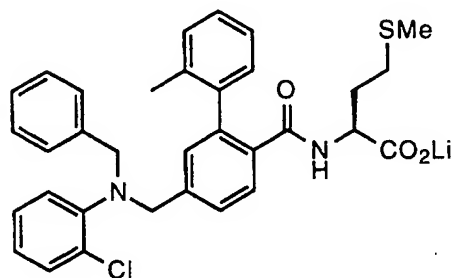


8605

Example 845

N-[4-N-(N-benzyl-N-(3-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H
 8610 NMR (d₆-DMSO): δ 1.48-1.74 (br comp, 2 H), 1.85-2.08 (comp, 8 H), 2.43 (s, 3 H),
 3.62-3.74 (br, 1 H), 4.78 (s, 2 H), 4.84 (s, 2 H), 6.90-7.04 (comp, 2 H), 7.07-7.36
 (comp, 13 H), 7.51 (d, J= 7.8 Hz, 1 H)

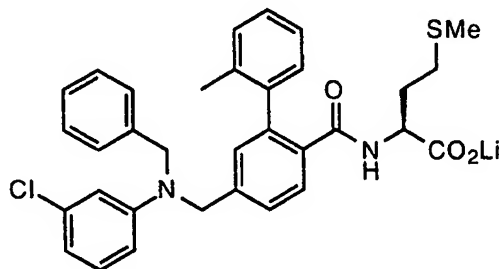


8615

Example 846

N-[4-N-(N-benzyl-N-(2-chlorophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H
 8620 NMR (d₆-DMSO): ¹H NMR (d₆-DMSO): δ 1.46-1.64 (br comp, 2 H), 1.76-2.03 (comp, 8
 H), 3.15-3.19 (br, 1 H), 4.23 (s, 2 H), 4.26 (s, 2 H), 6.84-7.47 (comp, 16 H).

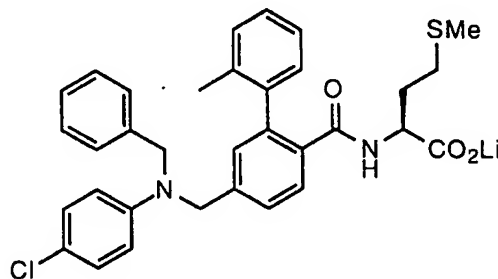


8625

Example 847

N-[4-*N*-(*N*-benzyl-*N*-(3-chlorophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.75 (br comp, 2 H), 1.88-2.10 (comp, 8 H), 3.64-3.75 (br, 1 H), 4.74 (s, 2 H), 4.79 (s, 2 H), 6.57-6.66 (comp, 3 H), 6.90-7.36 (comp, 12 H), 7.52 (d, *J* = 7.7 Hz, 1 H).

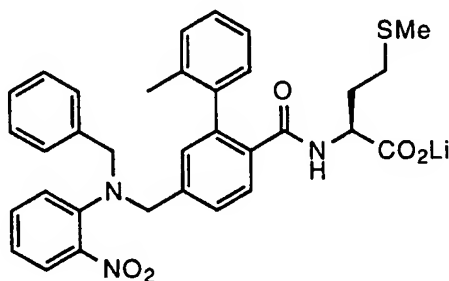


8635

Example 848

N-[4-*N*-(*N*-benzyl-*N*-(4-chlorophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.47-1.76 (br comp, 2 H), 1.89-2.10 (comp, 8 H), 3.65-3.77 (br, 1 H), 4.71 (s, 2 H), 4.77 (s, 2 H), 6.62-6.89 (comp, 2 H), 6.90-7.34 (comp, 13 H), 7.51 (d, *J* = 7.8 Hz, 1 H).



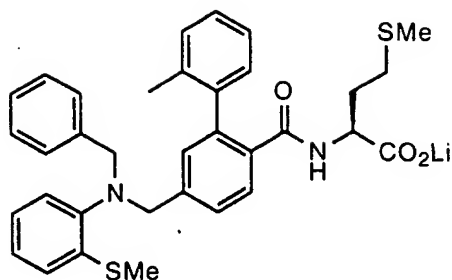
8645

Example 849

N-[4-*N*-(*N*-benzyl-*N*-(2-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.46-1.71 (br comp, 2 H), 1.86-2.20 (br comp, 8 H), 3.58-3.70 (br, 1 H), 4.25 (s, 2 H), 4.27 (s, 2 H), 6.85-6.95 (br, 1 H), 6.98-7.36 (comp, 12 H), 7.45 (d, *J* = 7.8 Hz, 2 H), 7.75 (dd, *J* = 1.7, 8.2 Hz, 1 H).

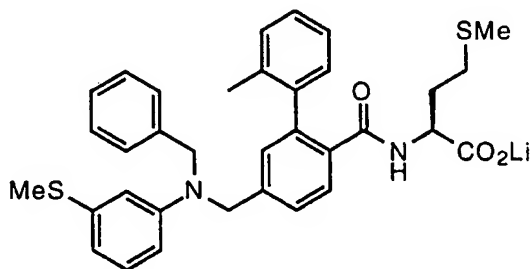
8650



Example 850

N-[4-(N-benzyl-N-(2-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

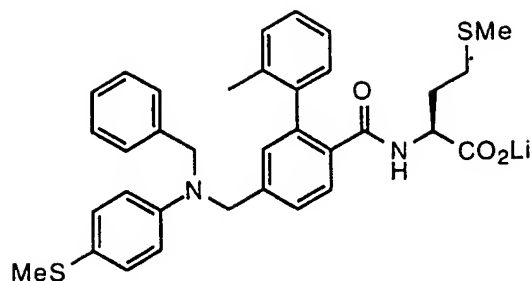
The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.72 (br comp, 2 H), 1.86-2.03 (br comp, 8 H), 2.40 (s, 3 H), 3.58-3.68 (br, 1 H), 4.09 (s, 2 H), 4.13 (s, 2 H), 6.83-6.91 (br, 1 H), 6.95-7.31 (comp, 11 H), 7.33-7.44 (comp, 4 H).



Example 851

N-[4-(N-benzyl-N-(3-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.72 (br comp, 2 H), 1.89-2.09 (br comp, 8 H), 2.27 (s, 3 H), 3.62-3.71 (br, 1 H), 4.71 (s, 2 H), 4.77 (s, 2 H), 6.45-6.49 (comp, 3 H), 6.91-7.35 (comp, 12 H), 7.50 (d, J = 8.1 Hz, 1 H).

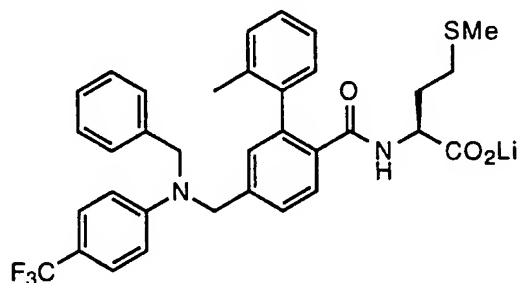


8675

Example 852*N*-[4-(*N*-benzyl-*N*-(4-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.45-1.74 (br comp, 2 H), 1.88-2.08 (br comp, 8 H), 2.33 (s, 3 H), 3.58-3.67 (br, 1 H), 4.70 (s, 2 H), 4.76 (s, 2 H), 6.64 (d, J = 8.8 Hz, 2 H), 6.88-6.94 (br, 1 H), 7.00 (s, 1 H), 7.10 (d, J = 8.8 Hz, 2 H), 7.16-7.34 (comp, 9 H), 7.50 (d, J = 7.8 Hz, 1 H).

8680

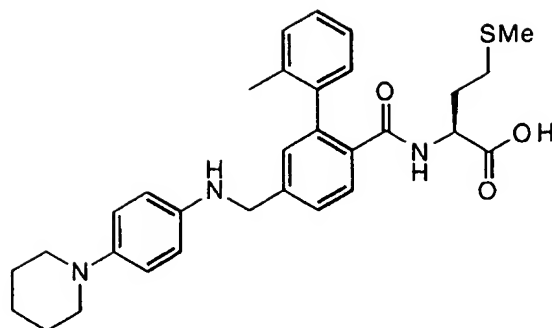


8685

Example 853*N*-[4-(*N*-benzyl-*N*-(4-trifluoromethylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157. ¹H NMR (d₆-DMSO): δ 1.48-1.75 (br comp, 2 H), 1.90-2.06 (br comp, 8 H), 3.64-3.74 (br, 1 H), 4.81 (s, 2 H), 4.86 (s, 2 H), 6.79 (d, J = 8.8 Hz, 2 H), 6.90-7.35 (comp, 11 H), 7.40 (d, J = 8.8 Hz, 2 H), 7.52 (d, J = 7.8 Hz, 1 H).

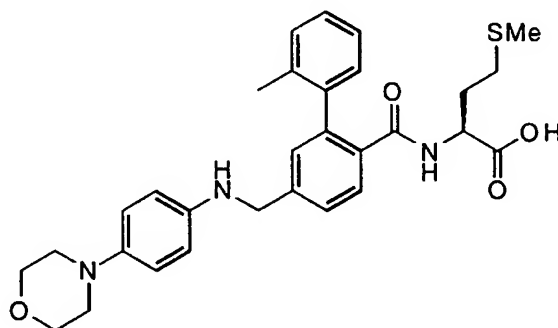
8690



8695

Example 862N-[4-N-(4-piperidin-1-yl)phenyl]aminomethyl-2-(2-methylphenyl)benzoyl]methionine

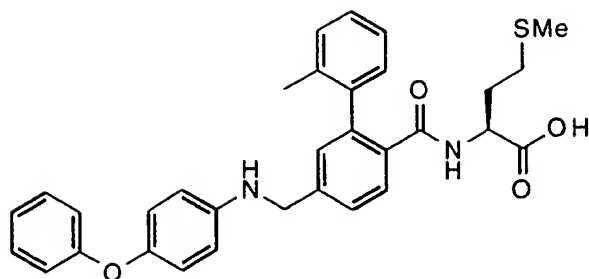
The desired compound was prepared according to the method of Example 158. MS
 m/e 530 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.55 (m, 3H), 1.78 (m, 4H), 1.85 (m,
 8700 1H), 2.0 (m, 8H), 3.03 (m, 4H), 4.3 (m, 3H), 6.13 (m, 1H), 6.54 (m, 2H), 6.98 (m, 2H),
 7.10-7.52 (m, 6H), 7.74 (m, 1H).



8705

Example 863N-[4-N-(4-morpholin-1-yl)phenyl]aminomethyl-2-(2-methylphenyl)benzoyl]methionine

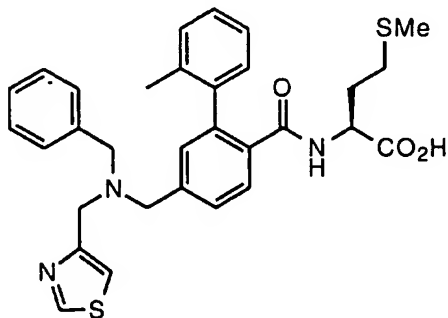
The desired compound was prepared according to the method of Example 158. MS
 m/e 534 (M+H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 1.48 (m, 1H), 1.83 (m, 1H), 2.0 (m,
 8H), 3.00 (m, 4H), 3.85 (m, 4H), 4.35 (m, 3H), 6.03 (m, 1H), 6.58 (m, 2H), 6.80 (m,
 8710 2H), 7.22 (m, 6H), 7.85 (m, 1H).

Example 864

8715 N-[4-N-(4-phenoxyphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. MS m/e 539 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.42 (m, 1H), 1.75 (m, 1H), 2.0 (m, 8H), 4.21 (m, 1H), 4.31 (s, 2H), 6.15 (m, 1H), 6.54 (m, 2H), 6.86 (m, 4H), 6.99 (m, 2H), 7.2 (m, 7H), 7.76 (m, 1H).

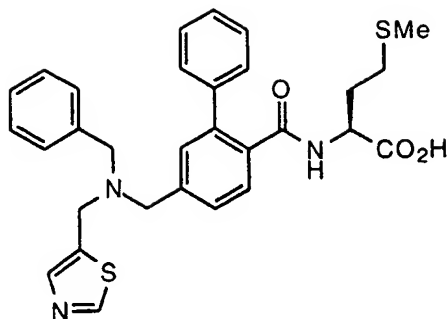
8720

Example 875

N-[4-N-(benzyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

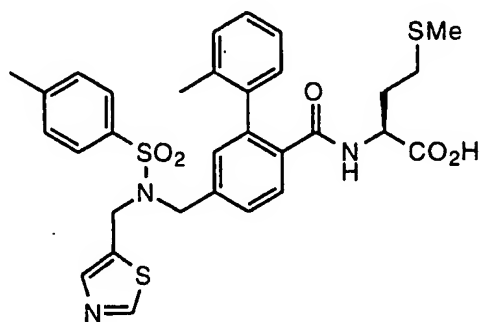
8725 The desired compound was prepared according to the method of Example 158. ¹H (300 MHz, DMSO d₆): δ 9.08, d, 1H; 8.13, d, 1H; 7.58, d, 1H; 7.49, s, 2H; 7.40, d, 2H; 7.31, t, 2H; 7.22, m, 4H; 7.11, m, 2H; 4.21, m, 1H; 3.77, s, 2H; 3.67, s, 2H; 3.62, s, 2H; 1.98 - 2.23, m, 5H; 1.97, s, 3H; 1.63 - 1.90, m, 2H. MS (ESI(-)): 558 (M-H). Calc'd for C₃₁H₃₃N₃O₃S₂ + 0.49 H₂O: C 65.49, H 6.02, N 7.39: Found: C 65.49, H 5.86, N 7.27.

8730

**Example 876**

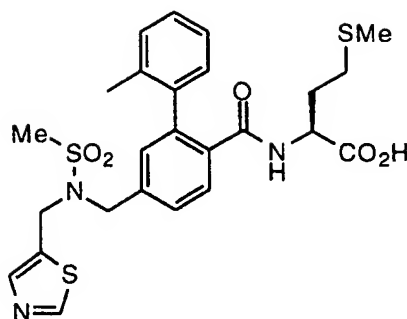
8735 N-[4-N-(benzyl-N-thiazol-5-ylmethyl)aminomethyl]-2-phenylbenzoyl]methionine

The desired compound was prepared according to the method of Example 158. ¹H (300 MHz, DMSO d₆): δ 9.04, s, 1H; 8.46, d, 1H; 7.82, s, 1H; 7.3, m, 13H; 4.27, ddd, 1H; 3.83, s, 2H; 3.64, s, 2H; 3.60, s, 2H; 2.21, m, 2H; 1.99, s, 3H; 1.84, m, 2H. MS (ESI(-)): 544 (M-H). Calc'd for C₃₀H₃₁N₃O₃S₂: C 66.03, H 5.72, N 7.70: Found: C 65.65, H 5.81, N 7.50.

**Example 877**

8745 N-[4-N-(toluenesulfonyl-N-thiazol-2-ylmethyl)aminomethyl]-2-(2-methylphenyl)-benzoyl]methionine

The desired compound was prepared according to the method of Example 157. ¹H (300 MHz, DMSO d₆): δ 12.62, bs, 1H; 8.94, s, 1H; 8.08, bs, 1H; 7.79, d, 2H; 7.59, s, 1H; 7.41, m, 3H; 7.20, m, 4H; 7.03, bs, 1H; 6.90, bs, 1H; 4.59, s, 2H; 4.38, s, 2H; 4.21, m, 1H; 2.51, s, 3H; 2.40, s, 3H; 2.18, m, 2H; 1.98, s, 3H; 1.78, m, 2H. MS (ESI(-)): 622 (M-H). Calc'd for C₃₁H₃₃N₃O₅S₃: C 59.69, H 5.33, N 6.74: Found: C 59.41, H 5.19, N 6.57.

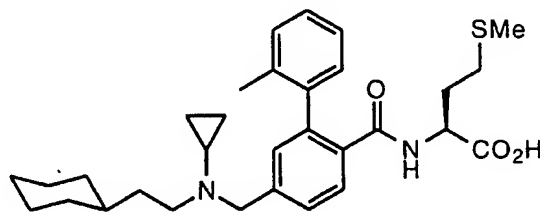


8755

Example 878N-[4-N-(methanesulfonyl)-N-thiazol-2-ylmethyl]aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

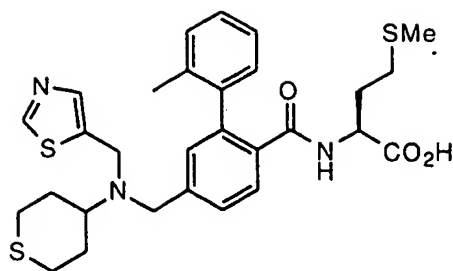
8760 The desired compound was prepared according to the method of Example 157. ¹H (300 MHz, DMSO d₆): δ 9.00, s, 1H; 8.11, bs, 1H; 7.52, s, 1H; 7.46, d, 1H; 7.39, dd, 1H; 7.00 - 7.22, m, 5H; 4.63, s, 2H; 4.42, s, 2H; 4.21, m, 1H; 3.02, s, 3H; 1.98 - 2.23, m, 5H; 1.97, s, 3H; 1.64 - 1.91, m, 2H. MS (ESI(-)): 546 (M-H); (ESI(+)): 548. Calc'd for C₂₅H₂₉N₃O₅S₃: C 54.82, H 5.34, N 7.67: Found: C 54.60, H 5.32, N .49.

8765

Example 880N-[4-(N-2-Cyclohexylethyl)-N-cyclopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine

8770 The desired compound was prepared according to the method of Example 158. ¹H (300 MHz, DMSO d₆): δ 8.06, d, 1H; 7.47, d, 1H; 7.31, dd, 1H; 7.20, m, 2H; 7.02 - 7.17, m, 3H; 4.21, m, 1H; 3.71, s, 2H; 2.50, m, 2H; 1.98 - 2.23, m, 6H; 1.97, s, 3H; 1.68 - 1.90, m, 3H; 1.50 - 1.66, m, 4H; 1.37, m, 2H; 1.03 - 1.14, m, 4H; 0.81, m, 2H; 0.44, m, 2H; 0.30, m, 2H. MS (ESI(-)): 521 (M-H); ESI((+)): 523 (MH⁺). Calc'd for C₃₁H₄₂N₃O₃S: C 71.23, H 8.10, N 5.36: Found: C 70.25, H 8.05, N 5.31.

8775



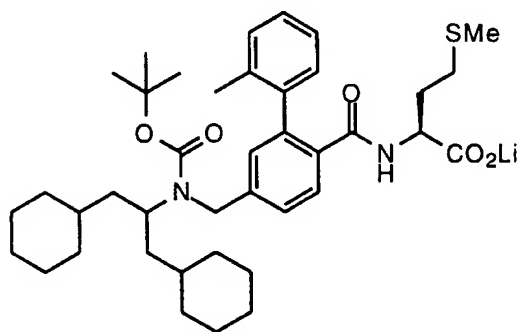
Example 881

8780

N-[4-(N-tetrahydrothiopyran-4-yl-N-thiazol-5-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

8785

The desired compound was prepared according to the method of Example 158. ¹H (300 MHz, DMSO d₆): δ 8.97, s, 1H; 8.08, d, 1H; 7.78, s, 1H; 7.44, dd, 2H; 7.00 - 7.25, m, 5H; 4.20, ddd, 1H; 3.89, s, 2H; 3.71, s, 2H; 2.38 - 2.70, m, 5H; 1.98 - 2.23, m, 7H; 1.97, s, 3H; 1.59 - 1.91, m, 4H. MS (ESI(-)): 5688 (M-H); ESI((+)): 570. Calc'd for C₂₉H₃₅N₃O₃S₃ + 0.45 H₂O: C 60.27, H 6.26, N 7.27; Found: C 60.27, H 6.32, N 7.17.



8790

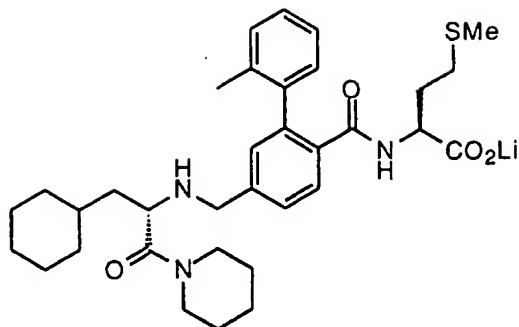
Example 886

N-[4-N-t-Butyloxycarbonyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine lithium salt

8795

The desired compound was prepared according to the method of Example 158, followed by treatment with di-t-butyl dicarbonate, and hydrolysis. ¹H NMR (300 MHz, DMSO) δ 0.68-0.87 (m, 4H), 0.95-1.10 (m, 13H), 1.28 (s, 3H), 1.40 (s, 6H), 1.50-1.70 (m, 13H), 1.94 (s, 3H), 1.97-2.18 (m, 5H), 3.55-3.70 (m, 1H), 4.20-4.40 (m, 3H), 6.85-6.95 (m, 1H), 7.01-7.27 (m, 5H), 7.30-7.42 (m, 1H), 7.42-7.53 (m, 1H). MS (APCI(+)) m/z 679 (M+H); Analysis calc'd for C₄₀H₅₇LiN₂O₅S•0.75H₂O: C, 68.79; H, 8.44; N, 4.01; found: C, 68.77; H, 8.33; N, 4.04.

8800

Example 887

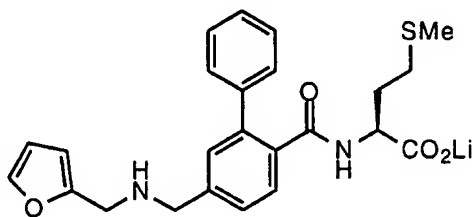
N-[4-N-(3-Cyclohexyl-1-oxo-1-piperidin-1-yl)propan-2-yl]aminomethyl-2-(2-
methylphenyl)benzoyl]-methionine lithium salt

8805

The desired compound was prepared according to the method of Example 158. ¹H NMR (300 MHz, DMSO) δ 0.65-0.90 (m, 2H), 1.00-1.24 (m, 10H), 1.30-1.70 (m, 15H), 1.90 (s, 3H), 1.92-2.18 (m, 5H), 3.35-3.80 (m, 3H), 6.85-6.95 (m, 1H), 7.06-7.23 (m, 5H), 7.32 (d, *J*=7.8 Hz, 1H), 7.46 (d, *J*=7.8 Hz, 1H). MS (ESI(-)) *m/z* 592 (M-H);

8810

Analysis calc'd for C₃₄H₄₆LiN₃O₄S•1.30H₂O: C, 65.53; H, 7.86; N, 6.74; found: C, 65.53; H, 7.36; N, 6.41.



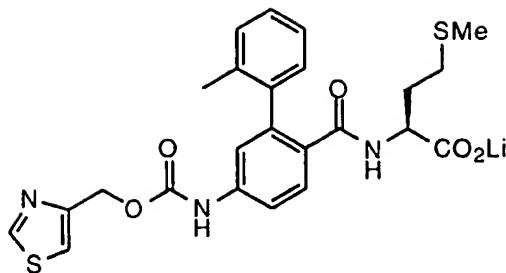
8815

Example 890

N-[4-(N-(furan-2-ylmethyl)aminomethyl)-2-phenylbenzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158. ¹H NMR (DMSO-*d*₆, 90 °C) δ 7.48-7.24 (m, 9 H), 7.07-7.04 (m, 1 H), 6.37-6.34 (m, 1 H), 6.24-6.20 (m, 1 H), 3.76-3.69 (m, 5 H), 2.43-2.16 (m, 3 H), 2.00-1.66 (m, 5 H); MS *m/z* 439 (M⁺ + 1, 100). Anal. Calcd for C₂₄H₂₅LiN₂O₄S•2H₂O (480.50): C, 59.99; H, 6.08; N, 5.83. Found: C, 59.83; H, 5.83; N, 5.74.

8820



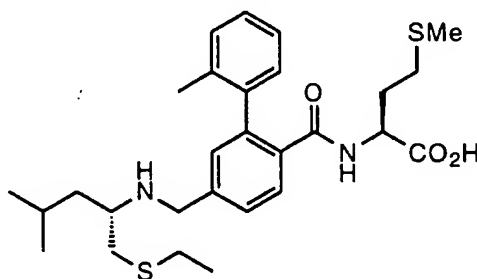
8825

Example 902

N-[4-N-(thiazol-5-ylmethoxycarbonyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

8830

The desired compound was prepared according to the method of Example 57. ¹H NMR (DMSO-*d*₆) δ 9.93 (s, 1 H), 9.04 (s, 1 H), 7.93 (s, 1 H), 7.44 (s, 2 H), 7.19-7.06 (m, 4 H), 6.92-6.88 (m, 1 H), 6.78-6.74 (m, 1 H), 5.34 (s, 2 H), 3.61-3.56 (m, 1 H), 2.10-1.79 (m, 8 H), 1.77-1.63 (m, 1 H), 1.60-1.53 (m, 1 H); MS *m/z* 498 (M⁺ - 1, 100). Exact mass calcd for C₂₄H₂₆N₃O₅S₂ 500.1303, found 500.1308.



8835

Example 905

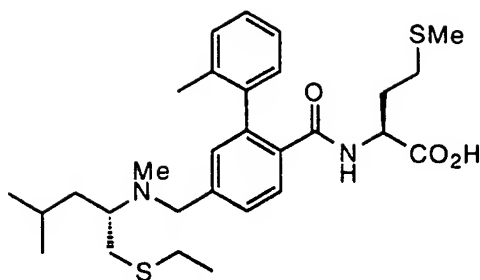
N-[4-(N-(1-ethylthio-4-methylpentan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]-methionine

8840

The desired compound was prepared according to the method of Example 158. ¹H (300MHz, CDCl₃, δ) 7.70 (1H, m), 7.43 (1H, d, *J*=10Hz), 7.30-7.00 (5H, m), 6.25 (1H, m), 4.38 (1H, m), 4.06 (1H, m), 3.91 (1H, bd, *J*=12Hz), 3.01 (1H, m), 2.82 (1H, dd, *J*=15&3Hz), 2.67 (1H, m), 2.45 (2H, q, *J*=8Hz), 2.05 (3H, s), 2.00 (3H, s), 2.00-1.80 (4H, m), 1.67 (1H, m), 1.53 (3H, m), 1.20 (3H, t, *J*=8Hz), 0.92 (3H, d, *J*=8Hz), 0.85 (3H, d, *J*=8Hz). *m/z* (ESI) 517 (MH⁺) Anal.calc. for C₂₈H₄₀N₂O₃S₂ C 65.08, H 7.80,

8845

N 5.42 Found C 65.37, H 7.86, N 5.38

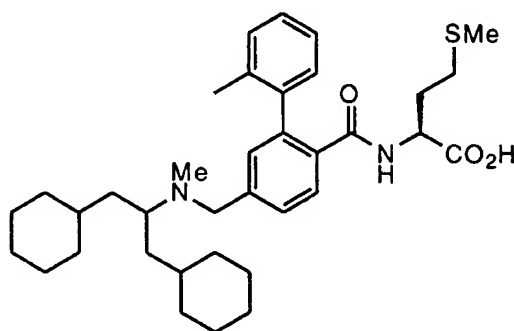


Example 906

8850 N-[4-(N-(1-ethylthio-4-methylpentan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine

The desired compound was prepared according to the method of Example 158. ¹H (300MHz, CDCl₃, δ) (rotamer) 7.70 (1H, m), 7.52 (1H, d, J=10Hz), 7.40-7.10 (5H, m), 6.08 (1H, m), 4.43 (1H, m), 3.88 (2H, m), 3.15 (1H, m), 2.87 (1H, dd, J=15&3Hz), 2.60 (1H, m), 2.51 (2H, q, J=8Hz), 2.38 (2.36) (3H, s), 2.06 (2.13) (3H, s), 2.00 (3H, s), 2.00-1.60 (4H, m), 1.60-1.40 (3H, m), 1.22 (3H, t, J=8Hz), 0.92 (3H, d, J=8Hz), 0.88 (3H, d, J=8Hz). m/z (ESI) 531 (MH⁺) Anal.calc. for C₂₉H₄₂N₂O₃S₂·0.25 H₂O C 65.07, H 8.00, N 5.23 Found C 65.01, H 7.84, N 5.14

8860

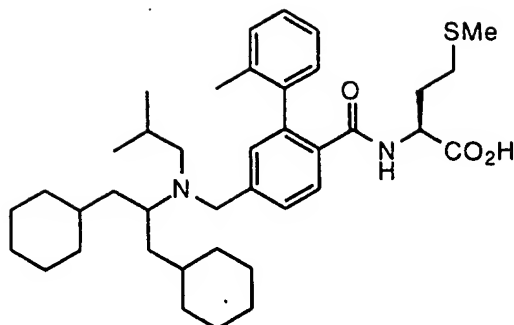


Example 907

N-[4-(N-(1,3-Dicyclohexylpropan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

8865 The desired compound was prepared according to the method of Example 158. ¹H (300MHz, DMSO-d₆, δ) 7.50 (1H, d, J=12Hz), 7.33 (1H, m), 7.25-7.10 (3H, m), 7.08 (1H, m), 6.98 (1H, m), 3.82 (1H, m), 3.55 (2H, m), 2.20-2.00 (3H, m), 2.08 (3H, s), 1.93 (3H, s), 1.82 (3H, s), 1.75-1.40 (12H, m), 1.40-1.20 (5H, m), 1.20-0.90 (9H, m), 0.90-0.70 (3H, m). m/z (ESI) 593 (MH⁺)

8870

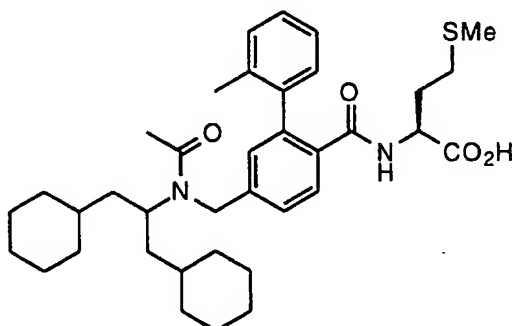
**Example 908**

N-[4-(*N*-(1,3-Dicyclohexylpropan-2-yl)-*N*-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine

8875

The desired compound was prepared according to the method of Example 158. ¹H (300MHz, DMSO-d₆, δ) (rotamer) 7.65 (1H, m), 7.49 (1H, bd, *J*=12Hz), 7.33 (1H, dd, *J*=12&2Hz), 7.30-7.00 (4H, m), 4.50 (2H, m), 4.10 (1H, m), 3.53 (1H, m), 3.20 (1H, m), 2.58 (1H, m), 2.20-2.00 (6H, m), 1.97 (1.92) (3H, s), 1.80-1.40 (14H, m), 1.40-1.20 (4H, m), 1.20-0.90 (8H, m), 0.90-0.60 (9H, d, *J*=9Hz). *m/z* (ESI) 635 (MH⁺) Anal.calc. for C₃₉H₅₈N₂O₃S·1.00 H₂O C 71.74, H 9.26, N 4.29 Found C 71.60, H 8.90, N 4.27

8880



8885

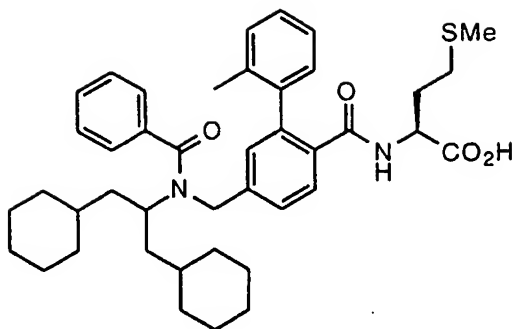
Example 909

N-[4-(*N*-acetyl-*N*-(1,3-Dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine

8890

The desired compound was prepared according to the method of Example 158, followed by Schotten-Baumann acylation and subsequent hydrolysis ¹H (300MHz, DMSO-d₆, δ) (rotamer) 12.60 (1H, m), 8.05 (1H, m), 7.48 (1H, m), 7.35 (1H, bd, *J*=12Hz), 7.20-6.90 (4H, m), 4.50 (2H, bd, *J*=18Hz), 4.22 (1H, m), 3.87 (1H, m), 3.10 (1H, m), 2.20-2.00 (4H, m), 2.08 (3H, s), 1.96 (1.94) (3H, s), 1.80 (3H, m), 1.60-1.30 (9H, m), 1.30-1.00 (14H, m), 0.80-0.60 (3H, m). *m/z* (ESI) 621 (MH⁺) Anal.calc. for C₃₇H₅₂N₂O₄S·0.50 H₂O C 70.55, H 8.48, N 4.45 Found C 70.67, H 8.42, N 4.36\

8895

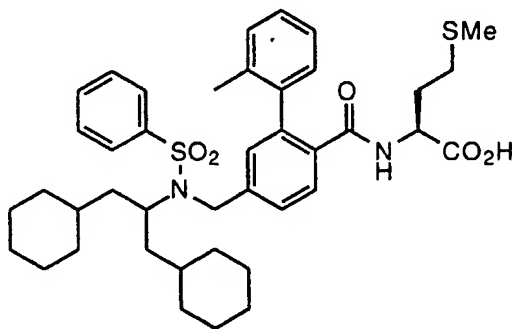
**Example 910**

N-[4-(N-benzoyl-N-(1,3-Dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine

8900

The desired compound was prepared according to the method of Example 909. ¹H (300MHz, DMSO-d₆, δ) 12.60 (1H, m), 8.05 (1H, bd, J=12Hz), 7.47 (4H, m), 7.33 (2H, m), 7.25-7.10 (5H, m), 4.62 (2H, bs), 4.21 (1H, m), 3.82 (1H, m), 3.10 (1H, m), 2.20-2.00 (4H, m), 1.96 (3H, s), 1.80 (3H, m), 1.60-1.30 (9H, m), 1.30-1.00 (14H, m), 0.80-0.60 (3H, m). m/z (ESI) 683 (MH⁺) Anal.calc. for C₄₂H₅₄N₂O₄S·0.75 H₂O C 72.43, H 8.03, N 4.02 Found C 72.24, H 7.72, N 3.93

8905



8910

Example 911

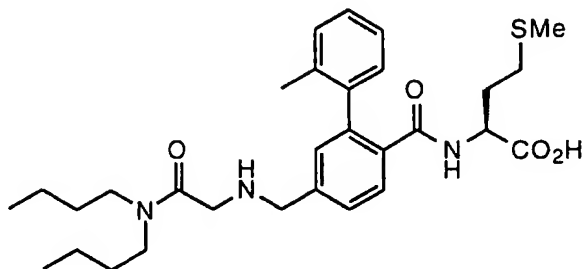
N-[4-(N-Benzenesulfoyl-N-(1,3-Dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine

8915

The desired compound was prepared according to the method of Example 157. ¹H (300MHz, DMSO-d₆, δ) 7.83 (2H, bd, J=12Hz), 7.80-7.55 (3H, m), 7.49 (2H, m), 7.30-7.00 (5H, m), 4.43 (2H, m), 4.22 (1H, m), 3.78 (1H, m), 3.20 (1H, m), 2.25-2.00 (4H, m), 1.97 (3H, s), 1.90-1.70 (3H, m), 1.60-1.40 (9H, m), 1.30-0.90 (14H, m), 0.80-0.40

(3H, m). m/z (ESI) 719 (MH^+) Anal.calc. for $C_{41}H_{54}N_2O_5S_2 \cdot 0.50 H_2O$ C 67.64, H 7.61, N 3.85 Found C 67.74, H 7.48, N 3.79

8920

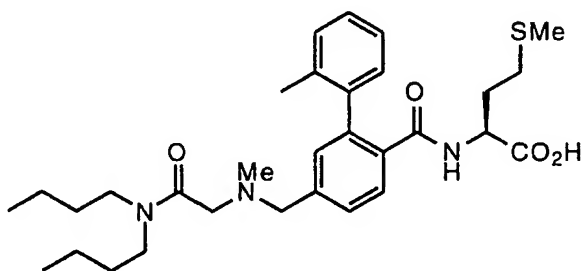


Example 912

N-[4-(N,N-dibutylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. 1H (300MHz, DMSO- d_6 , δ) 7.96 (1H, m), 7.48 (1H, d, $J=10Hz$), 7.39 (1H, dd, $J=12\&2Hz$), 7.25-7.00 (4H, m), 4.17 (1H, m), 3.80 (2H, s), 3.23 (2H, t, $J=8Hz$), 3.16 (2H, t, $J=8Hz$), 2.20-2.00 (5H, m), 1.96 (3H, s), 1.90-1.60 (2H, m), 1.41 (4H, m), 1.22 (4H, m), 0.85 (6H, q, $J=8Hz$). m/z (DCI, NH_3) 542 (MH^+) Anal.calc. for $C_{30}H_{43}N_3O_4S \cdot 0.75 H_2O$ C 64.89, H 8.08, N 7.57 Found C 64.83, H 7.94, N 7.33

8930



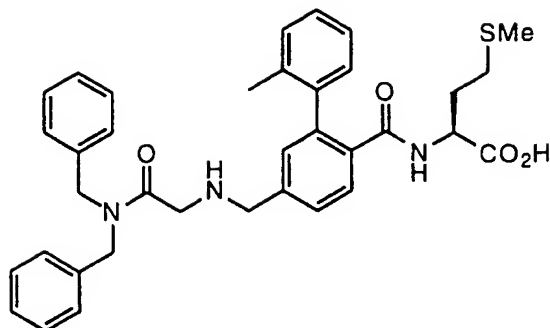
Example 913

N-[4-(N,N-dibutylacetamido)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

8935

The desired compound was prepared according to the method of Example 158. 1H (300MHz, DMSO- d_6 , δ) 7.53 (1H, d, $J=10Hz$), 7.38 (1H, dd, $J=12\&2Hz$), 7.25-7.00 (4H, m), 4.23 (1H, m), 3.64 (2H, s), 3.48 (1H, m), 3.35-3.16 (4H, m), 3.14 (1H, m), 2.22 (3H, s), 2.20-2.00 (5H, m), 1.96 (3H, s), 1.90-1.60 (2H, m), 1.42 (4H, m), 1.19 (4H, m), 0.86 (6H, q, $J=8Hz$). m/z (ESI) 556 (MH^+) Anal.calc. for $C_{31}H_{45}N_3O_4S$ C 66.99, H 8.16, N 7.56 Found C 66.65, H 8.20, N 7.23

8940

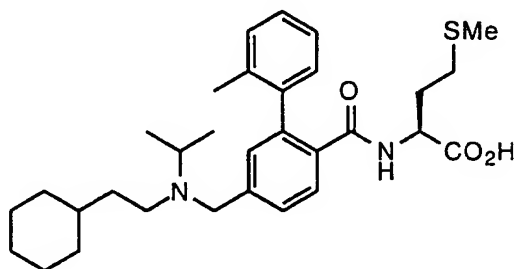


8945

Example 914*N*-[4-(*N*-(*N,N*-dibenzylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. ^1H (300MHz, DMSO- d_6 , δ) (rotamer) 7.76 (1H, m), 7.40 (1H, d, $J=9\text{Hz}$), 7.30-7.00 (15H, m), 4.41 (4H, d, $J=12\text{Hz}$), 4.10 (1H, m), 3.73 (2H, s), 3.41 (2H, s), 2.20-1.90 (5H, m), 1.87 (1.83) (3H, s), 1.80-1.50 (2H, m). m/z (ESI) 610 (MH^+)

8950

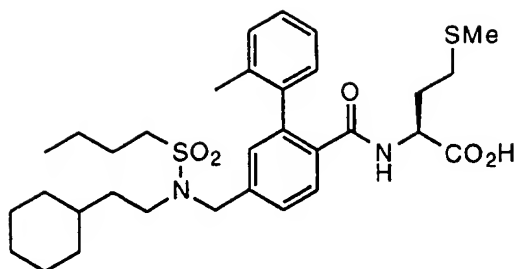
Example 915

8955

N-[4-(*N*-(2-Cyclohexylethyl)-*N*-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. ^1H (300MHz, CDCl_3 , δ) 7.80-7.60 (2H, m), 7.30-7.00 (5H, m), 6.50 (1H, d, $J=8\text{Hz}$), 4.38 (1H, m), 4.03 (2H, m), 3.67 (1H, m), 2.88 (2H, m), 2.20-2.00 (7H, m), 2.00 (3H, s), 1.80-1.40 (8H, m), 1.33 (6H, d, $J=7\text{Hz}$), 1.30-1.00 (3H, m), 1.00-0.80 (2H, m). m/z (ESI) 525 (MH^+) Anal. calc. for $\text{C}_{31}\text{H}_{44}\text{N}_2\text{O}_3\text{S}\cdot 0.50\text{H}_2\text{O}$ C 69.76, H 8.50, N 5.25 Found C 69.90, H 8.26, N 5.57

8960

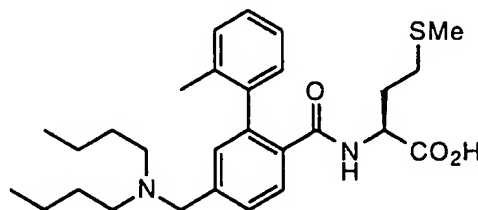


8965

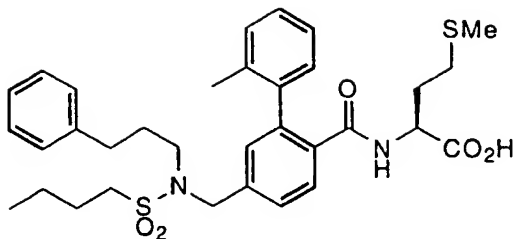
Example 916N-[4-(N-Butanesulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)]benzoyl]methionine

The desired compound was prepared according to the method of Example 157. ¹H
 8970 (300MHz, CDCl₃, δ) 7.99 (1H, m), 7.45 (1H, dd, J=9&2Hz), 7.40-7.10 (5H, m), 5.92
 (1H, m), 4.56 (1H, m), 4.44 (2H, s), 3.20 (2H, m), 2.96 (2H, m), 2.20-2.05 (5H, m),
 2.02 (3H, s), 2.00-1.70 (3H, m), 1.70-1.30 (10H, m), 1.30-1.00 (4H, m), 0.95 (3H, t,
 J=8Hz), 0.83 (2H, m). m/z (ESI) 603 (MH⁺) Anal.calc. for C₃₂H₄₆N₂O₅S₂·0.25 H₂O C
 63.28, H 7.72, N 4.61 Found C 63.27, H 7.73, N 4.50

8975

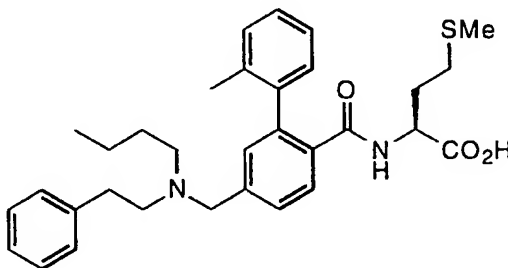
Example 917N-[4-(N,N-Dibutylaminomethyl)-2-(2-methylphenyl)]benzoyl]methionine

The desired compound was prepared according to the method of Example 158. ¹H
 8980 (300MHz, CDCl₃, δ) 7.75 (1H, d, J=9Hz), 7.67 (1H, m), 7.30-7.10 (5H, m), 6.33 (1H,
 m), 4.42 (1H, m), 4.13 (2H, m), 2.95 (4H, m), 2.20-2.00 (5H, m), 2.00 (3H, s), 2.00-
 1.80 (2H, m), 1.68 (4H, m), 1.33 (4H, m), 0.93 (6H, q, J=8Hz). m/z (DCI, NH₃) 485
 8985 (MH⁺) Anal.calc. for C₂₈H₄₀N₂O₃S·1.00 H₂O C 66.90, H 8.42, N 5.57 Found C 66.73,
 H 8.23, N 5.40

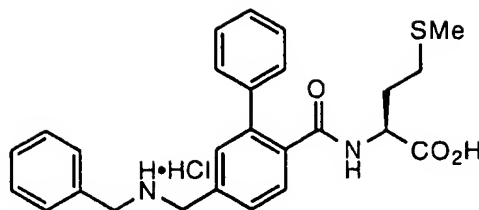
Example 927*N*-[4-(*N*-Butanesulfonyl-*N*-(3-phenylpropyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

8990 The desired compound was prepared according to the method of Example 157 ¹H
 (300MHz, CDCl₃, δ) 7.97 (1H, m), 7.40 (1H, dd, *J*=9&2Hz), 7.35-7.10 (8H, m), 7.04
 8995 (1H, d, *J*=2Hz), 7.03 (1H, s), 5.89 (1H, m), 4.60 (1H, m), 4.43 (2H, s), 3.22 (2H, t,
J=8Hz), 2.96 (2H, t, *J*=8Hz), 2.55 (2H, t, *J*=8Hz), 2.20-2.05 (2H, m), 2.05 (3H, s), 2.02
 (3H, s), 2.00-1.70 (5H, m), 1.57 (1H, m), 1.42 (2H, m), 0.94 (3H, t, *J*=8Hz). *m/z* (ESI)
 609 (MH⁺) Anal.calc. for C₃₃H₄₂N₂O₅S₂ C 64.89, H 6.93, N 4.59 Found C 64.61, H
 6.90, N 4.52

9000

Example 928*N*-[4-(*N*-Butyl-*N*-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

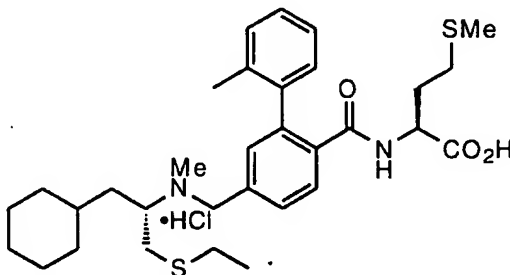
9005 The desired compound was prepared according to the method of Example 157 ¹H
 (300MHz, CDCl₃, δ) 7.78 (1H, d, *J*=9Hz), 7.60 (1H, bd, *J*=8Hz), 7.40-7.20 (5H, m),
 7.20-7.00 (5H, m), 6.27 (1H, m), 4.43 (1H, m), 4.20-4.00 (2H, m), 3.20-2.80 (6H, m),
 2.20-2.05 (5H, m), 1.98 (3H, s), 1.90 (1H, m), 1.63 (3H, m), 1.32 (2H, m), 0.93 (3H, t,
J=8Hz). *m/z* (ESI) 533 (MH⁺) Anal.calc. for C₃₂H₄₀N₂O₃S·1.00 H₂O C 69.79, H 7.69,
 9010 N 5.09 Found C 70.04, H 7.48, N 4.96

Example 936

9015 *N*-[4-(*N*-benzylaminomethyl)-2-phenylbenzoyl]methionine hydrochloride salt

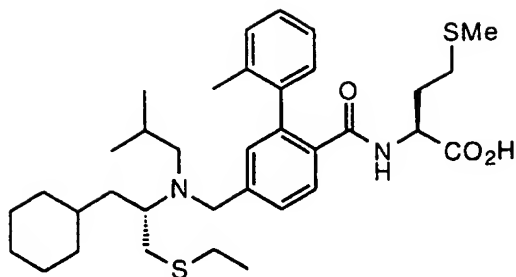
The desired compound was prepared according to the method of Example 158 (DMSO- d_6) δ 8.61 (d, 1H), 7.61 (m, 1H), 7.58 (m, 3H), 7.40 (m, 9H), 4.32 (m, 1H), 4.22 (s, 2H), 4.18 (s, 2H), 2.27 (m, 2H), 2.00 (s, 3H), 1.88 (m, 2H). MS (DCI/NH₃) 449 (M+H)⁺. Anal calcd for C₂₆H₂₉ClN₂O₃S · 0.80 H₂O: C, 62.53; H, 6.18; N, 5.61.

9020 Found: C, 62.59; H, 6.31; N, 5.57.

Example 944

9025 *N*-[4-*N*-(3-Cyclohexyl-1-ethylthiopropyl)-*N*-methylaminomethyl]-2-(2-methylphenyl)benzoyl]-methionine hydrochloride salt

The desired compound was prepared according to the method of Example 158 (DMSO- d_6) δ 8.23 (m, 1H), 7.75 (m, 1H), 7.59, 7.50 (both m, total 2H), 7.22, 7.15 (both m, total 4H), 4.50, 4.38 (both m, total 2H), 4.22 (m, 1H), 3.10, 2.90, 2.70 (all m, total 5H), 2.40, 2.10 (both m, total 7H), 1.98 (s, 3H), 1.90-1.40 (envelope, total 10H), 1.15, 1.00, 0.82 (all m, total 7H). MS (ESI) 569 (M-H)⁻. Anal calcd for C₃₂H₄₇ClN₂O₃S₂: C, 63.29; H, 7.80; N, 4.61. Found: C, 63.07; H, 7.79; N, 4.51.

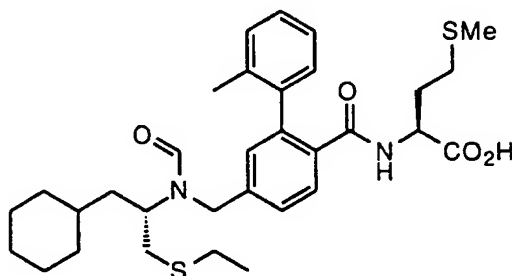


9035

Example 945**N-[4-N-(3-Cyclohexyl-1-ethylthiopropyl)-N-isobutylaminomethyl]-2-(2-methylphenyl)benzoyl-methionine**

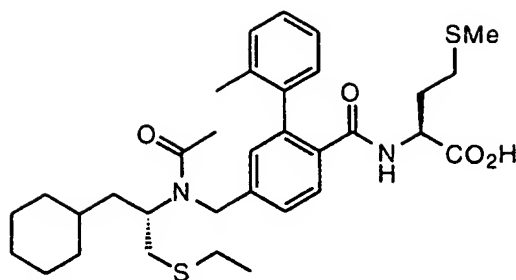
The desired compound was prepared according to the method of Example 158
 9040 (DMSO-d₆) δ 8.05 (d, 1H), 7.55 (d, 1H), 7.42 (d, 1H), 7.22, 7.20 (both m, total 5H), 4.27 (m, 1H), 3.73 (d, 1H), 3.60 (d, 1H), 2.90 (dd, 1H), 2.77 (m, 1H), 2.45 (q, 2H), 2.30, 2.10 (both m, total 8H), 2.00 (s, 3H), 1.97-1.25 (envelope, 11H), 1.19 (t, 3H), 1.19-0.70 (envelope, 12H). MS (ESI) 611 (M-H)⁻. Anal calcd for C₃₃H₅₂N₂O₃S₂ · 0.25 H₂O : C, 68.09; H, 8.57; N, 4.54. Found: C, 67.96; H, 8.53; N, 4.49.

9045

**Example 946****N-[4-N-(3-Cyclohexyl-1-ethylthiopropyl)-N-formylaminomethyl]-2-(2-methylphenyl)benzoyl-methionine**

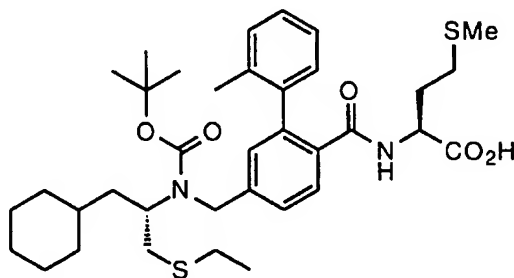
9050

The desired compound was prepared according to the method of Example 607,
 followed by Schotten-Baumann acylation. (DMSO-d₆) δ 8.40, 8.27 (both s, total 1H); 8.03, 7.97 (both d, total 1H), 7.45 (m, 2H), 7.20, 7.15 (both m, total 5H), 4.40 (m, 2H), 4.21 (m, 1H), 3.70 (m, 1H), 2.62, 2.46 (both m, total 4H), 2.18, 2.05 (both m, total 5H), 1.96
 9055 (s, 3H), 1.90-1.20 (envelope, 9H), 1.10, 1.00, 0.75 (all m, total 9H). MS (ESI) 585 (M-H)⁻. Anal calcd for C₃₂H₄₄N₂O₄S₂ : C, 65.72; H, 7.58; N, 4.79. Found: C, 65.47; H, 7.53; N, 4.74.

Example 947

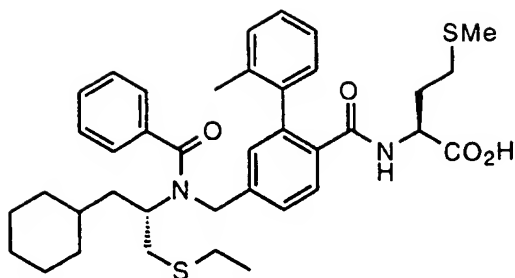
N-[4-N-acetyl-N-(3-Cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

The desired compound was prepared according to the method of Example 946
 (DMSO-d₆) δ 8.12, 8.00 (both d, total 1H), 7.55, 7.45, 7.40 (all m, total 2H), 7.20, 7.10, 7.06 (all m, total 5H), 4.65, 4.58 (both m, total 2H), 4.30, 4.20, 3.94 (all m, total 2H), 2.79, 2.60, 2.48 (all m, total 4H), 2.10, 1.97 (m, s, total 11H), 1.90-1.20 (envelope, 9H), 1.15, 1.10, 0.80 (all m, total 9H). MS (ESI) 597 (M-H)⁻. Anal calcd for C₃₃H₄₆N₂O₄S₂: C, 66.19; H, 7.74; N, 4.68. Found: C, 66.02; H, 7.68; N, 4.56.

Example 948

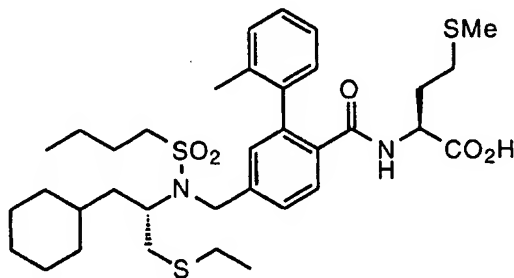
N-[4-N-t-Butyloxycarbonyl-N-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 946
 (DMSO-d₆) δ 7.95 (m, 1H), 7.46 (m, 1H), 7.38 (m, 1H), 7.20, 7.10 (both m, total 5H), 4.40, 4.30, 4.20 (all m, total 4H), 2.60, 2.47 (both m, total 4H), 2.10 (m, 5H), 1.97 (s, 3H), 1.90-1.00 (envelope, 25H), 0.78 (m, 2H). MS (ESI) 655 (M-H)⁻. Anal calcd for C₃₆H₅₂N₂O₅S₂: C, 65.82; H, 7.98; N, 4.26. Found: C, 65.56; H, 7.99; N, 4.20.

**Example 949**

9085 N-[4-N-Benzoyl-N-(3-Cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

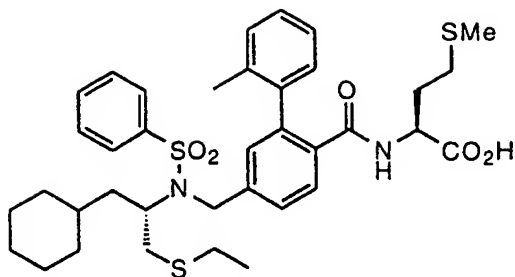
The desired compound was prepared according to the method of Example 946 (DMSO-d₆) δ 8.10 (d, 1H), 7.44 (m, 7H), 7.20 (m, 5H), 4.77, (d, 1H), 4.57 (d, 1H), 4.22 (m, 1H), 3.82 (m, 1H), 2.82 (m, 1H), 2.62 (m, 1H), 2.23, 2.10 (both m, total 7H), 1.97 (s, 3H), 1.80 (m, 2H), 1.48, 1.38 (both m, total 5H), 1.06, 0.65 (both m, total 11H).
 9090 MS (ESI) 659 (M-H)⁻. Anal calcd for C₃₈H₄₈N₂O₄S₂ : C, 69.06; H, 7.32; N, 4.24. Found: C, 68.94; H, 7.31; N, 4.17.

**Example 950**

9095 N-[4-N-Butanesulfonyl-N-(3-Cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

The desired compound was prepared according to the method of Example 157
 9100 (DMSO-d₆) δ 8.08 (d, 1H), 7.57 (s, 2H), 7.35, 7.25, 7.18 (all m, total 5H), 4.44 (m, 2H), 4.28 (m, 1H), 3.87 (m, 1H), 3.10 (m, 2H), 2.77, 2.64, 2.55 (all m, total 4H), 2.10 (m, 5H), 2.00 (s, 3H), 1.95-1.50 (envelope, 8H), 1.42, 1.30, 1.20, 1.10 (m, m, t, m, total 12H), 0.90 (t, 3H), 0.80 (m, 2H). MS (ESI) 675 (M-H)⁻. Anal calcd for C₃₅H₅₂N₂O₅S₃ : C, 62.10; H, 7.74; N, 4.14. Found: C, 61.86; H, 7.57; N, 4.18.

9105

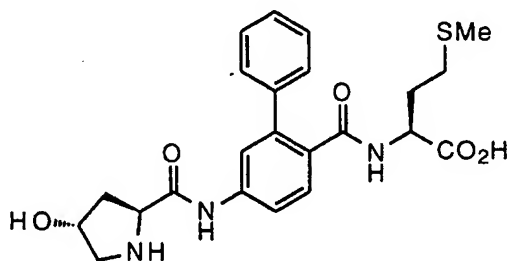
Example 951

N-[4-*N*-Benzenesulfonyl-*N*-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

9110

The desired compound was prepared according to the method of Example 157 (DMSO- d_6) δ 8.07 (d, 1H), 7.86 (d, 2H), 7.70 (m, 1H), 7.64 (m, 2H), 7.50 (s, 2H), 7.20 (m, 5H), 4.50 (m, 2H), 4.22 (m, 1H), 3.72 (m, 1H), 2.50-2.00 (envelope, 10H), 1.98 (s, 3H), 1.80 (m, 2H), 1.42, 1.20, 1.06, 0.90, 0.63 (m, m, t, m, m, total 15H). MS (ESI) 695 (M-H)⁻. Anal calcd for C₃₇H₄₈N₂O₅S₃: C, 63.76; H, 6.94; N, 4.02. Found: C, 63.63; H, 6.93; N, 3.94.

9115

Example 952

N-[4-(4-hydroxyprolinylamino)-2-phenylbenzoyl]methionine

9120

Example 952A

N-[4-*N*-(*N*-*t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxy-L-prolinyl)amino-2-phenylbenzoyl]-methionine methyl ester

9125

To a solution of *N*-*t*-butoxycarbonyl-4-*t*-butyldimethylsilyloxy-L-proline methyl ester (1.3 g, 3.6 mmol) in methanol (10 mL) was added 1N LiOH (5 mL) in an ice-bath. The reaction mixture was stirred for 30 min. The reaction mixture was adjusted to pH2-3 with 1N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned with dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1N HCl and water, dried over anhydrous

9130

magnesium sulfate, and concentrated in vacuo to give the corresponding acid **2** (1.05 g, 96 %) as a foamy solid. Without any purification, **2** (1.0 g, 3.29 mmol) was dissolved in 15 ml of dichloromethane. To this solution was added triethylamine (550 μ L, 3.9 mmol) in an ice-bath under argon, followed by IBCF (470 μ L, 3.6 mmol). The reaction mixture was allowed to stir for 40 min. At this time TLC showed the absence of the starting material. To this solution 4-amino-2-phenylbenzoyl methionine methyl ester² **3** (1.07 g, 2.97 mmol) in dichloromethane (10 mL) was introduced. The reaction mixture was stirred overnight, during which time the ice-bath expired. The reaction mixture was washed with 1N HCl, 5% sodium bicarbonate, and water, dried over magnesium sulfate, and solvent was removed. The residue was flash-chromatographed on silica gel using a 7:3 solution of hexanes and EtOAc to yield **4** (1.92 g, 94 %) as a foamy solid: mp 83°C; $[\alpha]^{25}_D$ -36.2 ($c=0.63$, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.94 (s, 1H), 7.53-7.26 (m, 8H), 6.41 (d, 1H, $J=6.0$ Hz), 4.55 (m, 4H), 3.63 (s, 3H), 3.57 (m, 1H), 3.32 (m, 1H), 2.30 (m, 1H), 2.05 (m, 2H), 1.94 (s, 3H), 1.83 (m, 1H), 1.73 (m, 1H), 1.45 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H); ¹³C NMR (CDCl₃) δ 171.8, 170.7, 169.3, 155.6, 140.0, 129.7, 129.0, 128.5, 128.2, 127.4, 120.2, 117.7, 80.7, 77.2, 70.1, 59.5, 54.7, 52.1, 51.7, 38.0, 30.9, 29.5, 28.2, 25.5, 17.7, 15.1, 4.9; HRMS (EI) calculated for C₃₅H₅₁N₃O₇SSi: 685.9498, found: 685.3217. ¹H NMR (300 MHz, CDCl₃+CD₃OD) δ 7.53-7.29 (m, 8H), 4.67 (m, 1H), 4.58 (s, 1H), 4.50 (m, 1H), 2.57 (m, 1H), 2.14 (m, 2H), 2.01 (s, 3H), 1.96 (m, 1H), 1.76 (m, 1H); ¹³C NMR (CD₃OD) δ 174.8, 172.6, 168.1, 142.4, 141.2, 140.6, 133.2, 130.0, 129.6, 129.5, 128.8, 122.2, 119.3, 71.2, 60.6, 55.2, 52.9, 39.9, 31.4, 30.9, 15.0.

Example 952B

N-[4-*N*-(*N*-*t*-butoxycarbonyl)-4-hydroxy-*L*-prolinyl]amino-2-phenylbenzoyl]methionine methyl ester

To a solution of the above compound (1.82 g, 2.65 mmol) in THF (20 mL) was added 1M TBAF (3 mL). The reaction mixture was stirred for overnight, diluted with EtOAc, and washed 3 times with water. The combined aqueous washings were extracted 3 times with EtOAc. The combined organic fractions were dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using ethyl acetate as an eluent to obtain **5** (864 mg, 57%) as a white solid: mp 121-123°C; $[\alpha]^{25}_D$ -53.3 ($c=0.43$, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.84 (s, 1H), 7.60-7.38 (m, 8H), 6.35 (br s, 1H), 4.58-4.51 (br s, 4H), 3.64 (s, 3H), 3.57 (m, 1H), 3.48 (m, 1H), 2.63 (m, 1H), 2.44 (br s, 1H), 2.07 (m, 2H), 1.98 (s, 3H), 1.86 (m, 1H), 1.72 (m, 1H), 1.44 (s, 9H); HRMS (EI) calculated for C₂₉H₃₇N₃O₇S: 571.6872, found: 571.2352.

Example 952C

N-[4-*N*-(4-hydroxy-L-prolinyl)amino-2-phenylbenzoyl]methionine trifluoroacetate (FTI-2103)

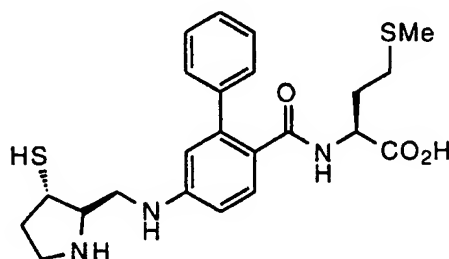
9170

9175

9180

9185

To a solution of the above compound (358 mg, 0.62 mmol) in methanol (6 mL) was added 1N LiOH (1 mL) in an ice bath. The reaction mixture was stirred for 4 hr. The reaction mixture was adjusted to pH=2-3 with 1N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned with chloroform and water, and extracted 3 times with chloroform. The combined organic solution was washed with 1N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give the resulting free acid (317 mg, 92 %) as a white solid. To a 5 ml of 1:1 solution of TFA and dichloromethane was added the acid (306 mg, 0.54 mmol). After 3 h, The reaction mixture was thoroughly evaporated in high vacuum to give an oily residue. The residue was triturate with anhydrous ether and the white solid was collected by filtration to give **6** (254 mg, 72%): HPLC 90% (purity); mp 127 (sub.), 154-157 °C (dec.); ¹H NMR (300 MHz, CDCl₃+CD₃OD) δ 7.53-7.29 (m, 8H), 4.67 (m, 1H), 4.58 (s, 1H), 4.50 (m, 1H), 2.57 (m, 1H), 2.14 (m, 2H), 2.01 (s, 3H), 1.96 (m, 1H), 1.76 (m, 1H); ¹³C NMR (CD₃OD) δ 174.8, 172.6, 168.1, 142.4, 141.2, 140.6, 133.2, 130.0, 129.6, 129.5, 128.8, 122.2, 119.3, 71.2, 60.6, 55.2, 52.9, 39.9, 31.4, 30.9, 15.0.



Example 959

9190

N-[4-((2*S*,4*S*)-4-thiolpyrrolidin-2-yl)methylamino]-2-phenylbenzoyl]methionine

Example 959A

N-[4-*N*-((2*R*,3*R*)-1-*t*-butyloxycarbonyl-3-*t*-butyldimethylsilyloxypyrrolidin-2-yl)methylamino]-2-phenylbenzoyl]methionine methyl ester

9195

To a solution of *N*-[4-amino-2-phenylbenzoyl]methionine methyl ester (238 mg, 0.66 mmol) and (2*R*,3*R*)-1-*t*-butyloxycarbonyl-3-*t*-butyldimethylsilyloxypyrrolidine-2-carboxaldehyde (158 mg, 0.48 mmol) in methanol (5 mL) was added acetic acid (0.5 mL), followed by sodium cyanoborohydride (65 mg, 1 mmol). The reaction mixture stirred overnight. After removal of the solvent, the residue was partitioned with ethyl acetate and 5%

9200 sodium bicarbonate, and extracted 3 times with ethyl acetate. The combined organic solution was washed with water and brine, dried over magnesium sulfate, and the solvent was removed. The residue was flash-chromatographed on silica gel using a 7:3 solution of hexanes and ethyl acetate to yield the title compound (284 mg, 88 %) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 7.68 (d, 1H, *J*=8.4 Hz), 7.40 (m, 6H), 6.62 (d, 1H), 6.44 (br s, 1H), 5.65 (d, 1H), 5.43 (s, 1H), 4.61 (m, 1H), 4.41 (br s, 1H), 4.08 (br s, 1H), 3.64 (s, 3H), 3.58-3.14 (m, 5H), 2.10 (t, 2H, *J*=7.7 Hz), 2.01 (s, 3H), 1.88 (m, 1H), 1.64 (m, 1H), 1.43 (s, 9H); 0.88 (s, 9H), 0.07 (s, 6H); HRMS (EI) calculated for C₃₅H₅₃N₃O₆SSi: 671.3424, found: 671.3415.

9210

Example 959B*N*-[4-*N*-((2*R*,3*R*)-1-*t*-butyloxycarbonyl-3-hydroxypyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine methyl ester

To a solution of the compound prepared in Example 959A (98 mg, 0.14 mmol) in THF (2 mL) was added 1M TBAF-THF (0.18 mL). The reaction mixture was stirred for 15 min at 0°C, diluted with ethyl acetate, and washed 3 times with water. The combined aqueous washings were extracted 3 times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a 3:1 solution of ethyl acetate and hexanes to obtain the title compound (60 mg, 76.8 %) as a white solid: mp 67 °C; [α]_D²⁵ +6.32 (*c*=0.19, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.61 (d, 1H, *J*=8.3 Hz), 7.30 (m, 6H), 6.59 (dd, 1H, *J*=1.2, 8.3 Hz), 6.43 (d, 1H, *J*=2.1 Hz), 5.74 (d, 1H, *J*=7.6 Hz), 5.44 (br s, 1H), 4.57 (m, 1H), 4.40 (m, 1H), 4.07 (br s, 2H), 3.59 (s, 3H), 3.37-3.16 (m, 5H), 2.04 (m, 2H), 1.96 (s, 3H), 1.87 (m, 1H), 1.65 (m, 1H), 1.43 (s, 9H); HRMS (EI) calculated for C₂₉H₃₉N₃O₆S: 557.2559, found: 557.2544.

9225

Example 959C*N*-[4-*N*-((2*R*,3*S*)-1-*t*-butyloxycarbonyl-3-acetylthiopyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine methyl ester

To a solution of the compound prepared in Example 959B (300 mg, 0.53 mmol) in THF (10 mL) were added TPP (278 mg, 1.06 mmol), followed by DIAD (208 μL, 1.06 mmol) at 0°C under argon. The mixture was allowed to stir for 30 min and thiolacetic acid (76 μL, 1.06 mmol) was added to this mixture at the same temperature. The reaction mixture was stirred overnight, during which time the ice-bath expired. The solution was concentrated. The crude products were chromatographed on silica gel using a 1:1 solution of hexanes and ethyl acetate to give the desired compound (211 mg, 64 %): ¹H NMR (300 MHz, CDCl₃) δ 7.68 (d, 1H, *J*=8.2 Hz), 7.39 (m, 6H), 6.64 (br s, 1H), 6.44 (br s, 1H),

5.66 (d, 1H, $J=7.4$ Hz), 5.39 (br s, 1H), 4.60 (m, 1H), 4.03-3.87 (m, 2H), 3.62 (s, 3H), 3.42-3.11 (m, 5H), 2.33 (s, 3H), 2.07 (t, 2H, $J=7.6$ Hz), 1.99 (s, 3H), 1.87 (m, 1H), 1.64 (m, 1H), 1.43 (s, 9H); HRMS (EI) calculated for $C_{31}H_{41}N_3O_6S_2$: 615.2436, found: 615.2437.

Example 959D

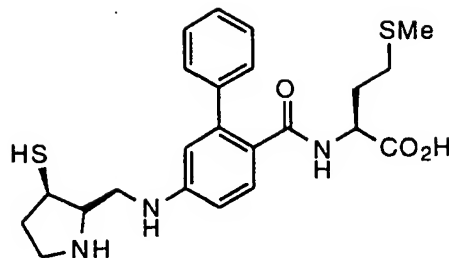
N-[4-*N*-((2*R*,3*S*)-3-acetylthiopyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine hydrobromide

To a solution of the compound prepared in Example 959C (106 mg, 0.17 mmol) in dichloromethane (10 mL) was added 1M boron tribromide-dichloromethane (2.58 mL) at 0° C under argon. The mixture was allowed to stir for 1 hr at the same temperature. Additionally the reaction mixture was stirred 4 hr at room temperature, and quenched by dropwise addition of water (5 mL). The solvent was removed to give crude residue. The residue was taken up with a 1:1 solution (1 mL) of water and THF, and purified by Prep-HPLC to give the desired 11 (83 mg, 73.7 %) as a white power: 1H NMR (300 MHz, CD_3OD) δ 7.48-7.35 (m, 6H), 7.01 (d, 1H, $J=8.6$ Hz), 6.64 (s, 1H), 4.45 (dd, 1H, $J=4.1, 9.2$ Hz), 3.92-3.81 (m, 2H), 3.69-3.65 (m, 1H), 3.55-3.40 (m, 4H), 2.55 (m, 1H), 2.32 (s, 3H), 2.22 (m, 1H), 2.09 (m, 1H), 2.05 (s, 3H), 1.97 (m, 1H), 1.79 (m, 1H).

Example 959E

N-[4-((2*S*,4*S*)-4-thiopyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine

To a solution of the compound described in Example 959D (80 mg, 0.12 mmol) in TFA (2 mL) was added mercuric acetate (0.38 g, 1.2 mmol) at 0° C under argon. The reaction mixture was allowed to stir for 30 min at the same temperature. This solution was evaporated and the resulting solid was suspended in methanol (10 mL). Gaseous hydrogen sulfide was bubbled into the reaction mixture for 15 min. The black precipitate was removed by filtration. After removing methanol, the residue was taken up with a 1:1 solution (1 mL) of water and THF, and purified by Prep-HPLC to afford the desired 12 (7.7 mg, 10.3 %) as a white powder: 1H NMR (300 MHz, CD_3OD) δ 7.45-7.39 (m, 6H), 6.74 (br s, 1H), 6.70 (br s, 1H), 4.44 (br s, 1H), 3.72-3.30 (m, 7H), 2.56 (br s, 1H), 2.18 (m, 1H), 2.02-1.96 (m, 2H), 2.01 (s, 3H), 1.80 (m, 1H).



9270

Example 960N-[4-((2S,4R)-4-thiolpyrrolidin-2-yl)methylamino]-2-phenylbenzoyl]methionineExample 960A

9275

(2R,3S)-1-Boc-2-*t*-butyldimethylsilyloxymethyl-3-benzoyloxypyrrolidine

To a solution of (2R,3S)-1-Boc-2-*t*-butyldimethylsilyloxymethyl-3-hydroxypyrrolidine (1.52 g, 4.59 mmol) in THF (20 mL) was added TPP (2.41 g, 9.2 mmol), followed by dropwise addition of DIAD (1.82 mL, 9.2 mmol) in THF (10 mL) at 0°C under argon atmosphere. The mixture was allowed for 40 min and benzoic acid (1.12 g, 9.2 mmol) was added dropwisely to this mixture at the same temperature. The reaction mixture was stirred overnight, during which time the ice bath expired. The solvent was removed, and a 3:1 solution of hexanes and ethyl acetate was introduced to the resulting residue to precipitate the insoluble by-products. After removal of by-products, the solution was concentrated. The crude product was chromatographed on silica gel using a 9:1 solution of hexanes and ethyl acetate to yield 14 (1.3 g, 65 %) as a foamy solid: ¹H NMR (300 MHz, CDCl₃) δ 7.55-7.32 (m, 5H), 5.49 (dd, 1H, *J* = 4.2, 11.7 Hz), 3.98-3.52 (m, 5H), 2.40 (m, 1H), 2.07 (m, 1H), 1.47 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); MS (EI) *m/z* (relative intensity) 379 ([M-C₄H₈]⁺, 15), 322 (50), 154 (50), 105 (90), 77 (80).

9290

Example 960B(2R,3S) 1-Boc-2-*t*-butyldimethylsilyloxymethyl-3-hydroxypyrrolidine

To a solution of the compound prepared in Example 960A (1.25 g, 2.86 mmol) in methanol (5 mL) was added 1N LiOH (3 mL) in an ice-bath. The reaction mixture was stirred for 2 hr. The reaction mixture was adjusted to pH2-3 with 1N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned with dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic fractions were dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a 3:1 solution of hexanes and ethyl acetate to obtain the desired compound (275 mg, 30%) as a white solid: mp 118°C; [α]_D²² -46.7 (*c*=0.47, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 4.34 (s, 1H), 3.77 (dd, 1H,

9300

$J = 3.0, 9.8$ Hz), 3.66-3.29 (m, 4H), 2.54 (d, 1H, $J = 8.5$ Hz), 2.09 (m, 1H), 1.79 (m, 1H), 1.42 (s, 9H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (CDCl_3 , minor isomer) δ 154.8, 79.7 (79.3), 74.6 (74.1), 67.0 (67.1), 63.2 (62.5), 44.7 (45.2), 31.7 (32.5), 28.7, 26.0, 18.3, -5.2; MS (EI) m/z (relative intensity) 275 ($[\text{M}-\text{C}_4\text{H}_8]^+$, 20), 259 (85), 218 (100), 86 (40), 75 (55), 57 (90).

Example 960C

(2R,3S) 1-Boc-2-*t*-butyldimethylsilyloxymethyl-3-*t*-butyldimethylsilyloxypyrrolidine

To a solution of the compound prepared in Example 960B (198 mg, 0.59 mmol) in dry DMF (2 mL) were added *tert*-butyldimethylsilyl chloride (110 mg, 0.71 mmol) and imidazole (102 mg, 1.5 mmol). The reaction mixture was stirred for 5 hr and then diluted with ether (20 mL). The reaction mixture was washed with brine, 1M HCl, and 5 % sodium bicarbonate. The organic layer was dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a 9:1 solution of hexanes and ethyl acetate to obtain the title compound (235 mg, 88%): ^1H NMR (300 MHz, CDCl_3) δ 4.27 (m, 1H), 3.62-3.20 (m, 5H), 1.88 (m, 1H), 1.62 (m, 1H), 1.36 (s, 9H), 0.78 (s, 18H), -0.03 (s, 12H); MS (CI, isobutane) m/z (relative intensity) 446 ($[\text{M}+\text{H}]^+$, 60), 390 (10), 346 (100).

Example 960D

(2R,3S) 1-Boc-2-hydroxymethyl-3-*t*-butyldimethylsilyloxypyrrolidine

To a solution of the compound prepared in Example 960C (229 mg, 0.51 mmol) in THF (2 mL) at 0°C were added water (2 mL) and acetic acid (6 mL). The reaction mixture was stirred for overnight at room temperature. After this time, the reaction mixture was concentrated under reduced pressure. The excess water was removed by azeotrope with toluene. The crude product was purified by flash chromatography on silica gel using a 9:1 solution of hexanes and ethyl acetate to obtain the title compound (96 mg, 56.8%): ^1H NMR (300 MHz, CDCl_3) δ 4.41 (br s, 1H), 4.00 (s, 1H), 3.66-3.27 (m, 5H), 1.88 (m, 1H), 1.70 (m, 1H), 1.42 (s, 9H), 0.83 (s, 9H), 0.03 (s, 6H).

Example 960E

N-4-[(2R,3S) 1-Boc-3-*t*-butyldimethylsilyloxypyrrolidin-2-yl]methylamino)-2-phenylbenzoyl]methionine methyl ester

To a solution of DMSO (42 μL , 0.58 mmol) in dichloromethane (2 mL) were added trifluoroacetic anhydride (62 μL , 0.43 mmol) via syringe at -78 °C under the slight stream of argon. After 10 min, the compound prepared in Example 960D (96 mg, 0.29 mmol) in dichloromethane (2 mL) was added to this mixture at the same temperature. The reaction

mixture was stirred for 1 hr. To this solution was added triethylamine (122 μ l, 0.87 mmol). The reaction mixture was allowed for 1 hr at -78°C , slowly warmed to room temperature and concentrated. After usual work-up, the crude aldehyde was used for the next step without purification. To a solution of N-[4-amino-2-phenylbenzoyl]methionine methyl ester hydrochloride (172 mg, 0.29 mmol) and the aldehyde in methanol (5 mL) were added acetic acid (0.5 mL), followed by sodium cyanoborohydride (38 mg, 0.58 mmol). The reaction mixture was allowed to react for overnight. After removal of the solvent, the residue was partitioned with ethyl acetate and 5% sodium bicarbonate, and extracted 3 times with ethyl acetate. The combined organic solution was washed with water and brine, dried over magnesium sulfate, and the solvent was removed. The residue was flash-chromatographed on silica gel using a 1:1 solution of hexanes and ethyl acetate to yield the title compound (142 mg, 73 %) as a oily residue: ^1H NMR (300 MHz, CDCl_3) δ 7.64 (d, 1H, $J=8.0$ Hz), 7.35 (m, 6H), 6.55 (d, 1H, $J=8.2$ Hz), 6.37 (br s, 1H), 5.67 (d, 1H, $J=7.6$ Hz), 5.55 (s, 1H), 4.56 (m, 1H), 4.21-3.15 (m, 7H), 3.59 (s, 3H), 2.04 (t, 2H, $J=7.7$ Hz), 1.95 (s, 3H), 1.83 (m, 1H), 1.60 (m, 1H), 1.42 (s, 9H); 0.82 (s, 9H), -0.03 (s, 6H); ^{13}C NMR (CDCl_3 , minor isomer) δ 172.1, 168.6, 156.6, 155.0, 150.1 (149.6), 147.7 (141.4), 131.4, 128.8 (128.6), 127.7, 122.6 (122.5), 113.5 (113.7), 110.9, 79.9 (80.2), 74.5, 64.9 (64.7), 60.4, 52.3, 51.8, 47.6, 45.2 (44.8), 33.1, 31.6 (31.9), 29.5, 28.4, 25.7, 21.0, 18.0, 15.3, 14.2, -4.6.

Example 960F

N-4-[(2R,3S) 1-Boc-3-hydroxypyrrolidin-2-ylmethyl]amino)-2-phenylbenzoyl]methionine methyl ester

To a solution of the compound prepared in Example 960E (140 mg, 0.20 mmol) in THF (3 mL) was added 1M TBAF-THF (0.3 mL). The reaction mixture was stirred for 30 min at 0°C and then quenched with saturated ammonium chloride. The reaction mixture was diluted with ethyl acetate, and washed 3 times with water. The combined aqueous washings were extracted 3 times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a 1:1 solution of ethyl acetate and hexanes to obtain the desired compound (85 mg, 76 %) as a oily residue: ^1H NMR (300 MHz, CDCl_3) δ 7.55 (d, 1H, $J=8.3$ Hz), 7.30 (m, 6H), 6.45 (d, 1H, $J=8.5$ Hz), 6.31 (br s, 1H), 5.75 (br s, 1H), 5.54 (br s, 1H), 4.51 (m, 1H), 4.15-3.82 (m, 3H), 3.56 (s, 3H), 3.59-2.98 (m, 5H), 2.00 (m, 2H), 1.92 (s, 3H), 1.80 (m, 1H), 1.56 (m, 1H), 1.38 (s, 9H).

Example 960G

N-4-[(2R,3R) 1-Boc-3-acetylthiopyrrolidin-2-ylmethyl]amino)-2-phenylbenzoyl]methionine
methyl ester

9375

To a solution of the compound prepared in Example 960F (85 mg, 0.15 mmol) in THF (3 mL) were added TPP (80 mg, 0.30 mmol), followed by DIAD (60 μ L, 0.30 mmol) at 0° C under argon. The mixture was allowed to stir for 30 min and thiolacetic acid (22 μ L, 0.31 mmol) was added to this mixture at the same temperature. The reaction mixture was stirred overnight, during which time the ice-bath expired. The solution was concentrated. The crude products were chromatographed on silica gel using a 1:1 solution of hexanes and ethyl acetate to give the desired compound (80 mg, 86.6 %) as a oily residue: ¹H NMR (300 MHz, CDCl₃) δ 7.65 (d, 1H, *J*=9.0 Hz), 7.37 (s, 5H), 6.55 (d, 1H, *J*= 7.7 Hz), 6.37 (s, 1H), 5.66 (d, 1H, *J*=7.3 Hz), 5.44 (br s, 1H), 4.58 (m, 1H), 4.40-3.98 (m, 3H), 3.60 (s, 3H), 3.38-3.06 (m, 3H), 2.32 (s, 3H), 2.21 (m, 1H), 2.07 (t, 2H, *J*=7.6 Hz), 1.99 (s, 3H), 1.87 (m, 1H), 1.64 (m, 1H), 1.43 (s, 9H); ¹³C NMR (CDCl₃) δ 194.4, 172.2, 168.5, 156.0, 150.1, 141.8, 141.4, 131.4, 128.8, 128.7, 127.8, 122.2, 113.4, 111.0, 80.5, 60.4, 57.6, 52.4, 51.8, 46.3, 45.1, 44.8, 42.3, 31.7, 30.7, 29.5, 28.4, 15.3, 14.7; HRMS (EI) calculated for C₃₁H₄₁N₃O₆S₂: 615.2436, found: 615.2436.

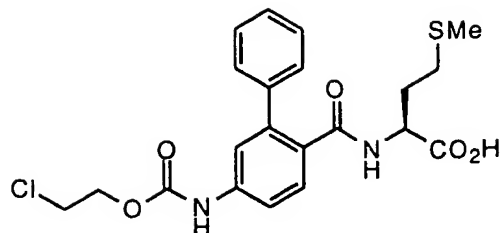
9390

Example 960H

N-4-[(2R,3R) 3-thiopyrrolidin-2-ylmethyl]amino)-2-phenylbenzoyl]methionine
hydrobromide

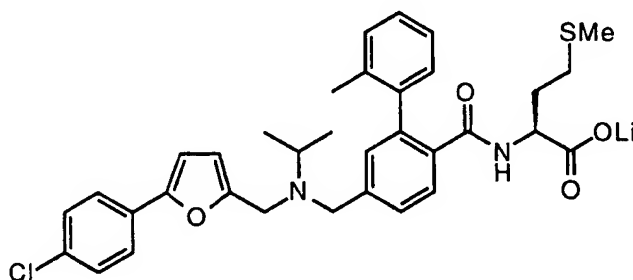
To a solution of the compound prepared in Example 960G (78 mg, 0.12 mmol) in dichloromethane (5 mL) was added 1M boron tribromide-dichloromethane (1.2 mL) at 0° C under argon. The mixture was allowed to stir for 1 hr at the same temperature. Additionally the reaction mixture was stirred 4 hr at room temperature, and quenched by dropwise addition of water (5 mL). The solvent was removed to give crude residue. Without purification, the crude thioacetate was dissolved in TFA (2 mL). To this solution, mercuric acetate (0.1 g, 0.31 mmol) was added at 0° C under argon. The reaction mixture was allowed to stir for 30 min at the same temperature. This solution was evaporated and the resulting solid was suspended in methanol (10 mL). Gaseous hydrogen sulfide was bubbled into the reaction mixture for 5 min. The black precipitate was removed by filtration. After removing methanol, the residue was taken up with a 1:1 solution (1 mL) of water and THF, and purified by Prep-HPLC to afford the desired compound (17 mg, 23 %) as a white powder: ¹H NMR (300 MHz, CD₃OD) δ 7.46-7.34 (m, 6H), 6.74 (m, 1H), 6.66 (s, 1H), 4.46 (m, 1H), 4.10-3.91 (m, 2H), 3.75-3.31 (m, 4H), 2.56-2.40 (m, 2H), 2.20-1.78 (m, 4H), 2.01 (s, 3H).

9410

**Example 979****N-[4-(N-2-chloroethoxycarbonyl)amino-2-phenylbenzoyl]methionine**

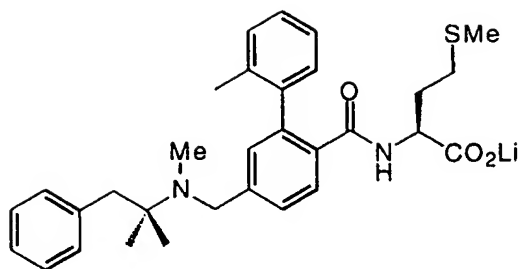
The desired compound was prepared according to the method of Example 57 ¹H
 9415 NMR (CD₃OD): δ 1.68-1.82 (m, 1 H), 1.86-2.03 (comp, 4 H), 2.03-2.26 (comp, 2 H),
 3.28 (m, 2 H), 3.72 (t, *J* = 5.8 Hz, 2 H), 4.44 (dd, *J* = 4.4, 9.2 Hz, 1 H), 6.58 (d, *J* = 2.3
 Hz, 1 H), 6.66 (dd, *J* = 2.3, 8.5 Hz, 1 H), 7.27-7.46 (comp, 8 H). LRMS (CI): 389 (M-
 62, loss of COCl)⁺.

9420

**Example 980****N-[4-(N-5-(4-Chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Example 158 ¹H
 9425 NMR (300 MHz, d₆ DMSO) δ 7.59 - 7.55 (m, 2H), 7.44 (d, 1H), 7.42 - 7.36 (m, 3H),
 7.24 - 7.06 (m, 5H), 6.88 (d, 1H), 6.36 (d, 1H), 3.69 (s, 2H), 3.65 (s, 2H), 2.96 (m,
 1H), 2.16 - 1.50 (m, 11H) 1.04 (d, 6H) Calcd for the acid C₃₄H₃₆O₄N₂SCl APCI -Q1MS,
 MH- 603.

9430

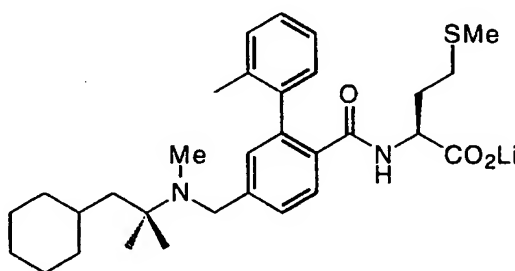
**Example 982**

N-[4-(N-Methyl-N-(1,1-dimethyl-2-phenylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine lithium salt

9435

The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 1.02 (s, 6H), 1.52-1.76 (m, 4H), 1.94 (s, 3H), 1.96-2.04 (m, 3H), 2.17 (s, 3H), 2.78 (s, 2H), 3.64-3.73 (m, 3H), 6.92 (d, J=5.0 Hz, 1H), 7.05-7.23 (m, 10H), 7.34 (dd, J=7.8, 1.5 Hz, 1H), 7.47 (d, J=7.8 Hz, 1H). MS (APCI(+)) m/z 518 (M+H); Analysis calc'd for C₃₁H₃₇LiN₂O₃S+0.85H₂O: C, 68.96; H, 7.22; N, 5.19; found: C, 68.86; H, 6.60; N, 5.25.

9440

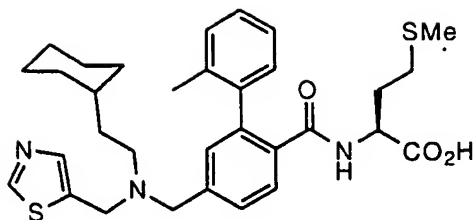
**Example 983**

N-[4-(N-Methyl-N-(1,1-dimethyl-2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine lithium salt

9445

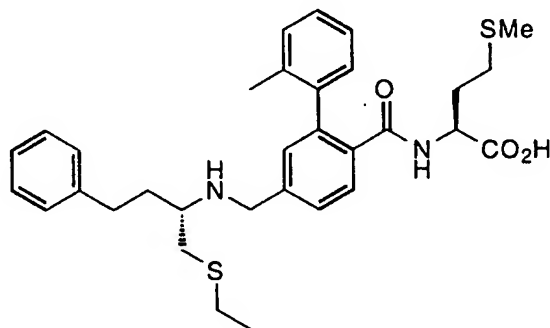
The desired compound was prepared according to the method of Example 158 ¹H NMR (300 MHz, DMSO) δ 0.85-1.17 (m, 6H), 1.03 (brs, 6H), 1.30-1.35 (m, 2H), 1.51-1.77 (m, 10H), 1.93 (s, 3H), 1.97-2.18 (m, 3H), 2.02 (s, 3H), 3.56 (brs, 2H), 3.59-3.74 (m, 1H), 6.92 (d, J=5.0 Hz, 1H), 7.11-7.23 (m, 5H), 7.34 (d, J=7.7 Hz, 1H), 7.46 (d, J=7.8 Hz, 1H). MS (APCI(+)) m/z 525 (M+H); Analysis calc'd for C₃₁H₄₃LiN₂O₃S+0.80H₂O: C, 68.31; H, 8.25; N, 5.14; found: C, 68.29; H, 8.23; N, 5.04.

9455

Example 986

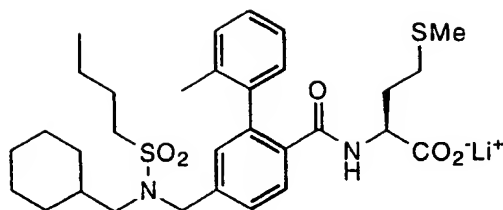
N-[4-(N-2-Cyclohexylethyl)-N-thiazol-5-ylmethylaminomethyl]-2-(2-methylphenyl)benzoyl]-methionine

The desired compound was prepared according to the method of Example 157 ¹H nmr (300 MHz, DMSO d₆): δ 9.02, s, 1H; 8.09, d, 1H; 7.76, s, 1H; 7.48, d, 1H; 7.37, dd, 1H; 7.21, m, 2H; 7.15, m, 3H; 4.21, m, 1H; 3.83, s, 2H; 3.61, s, 2H; 2.42, t, 2H; 1.98 - 2.23, m, 6H; 1.96, s, 3H; 1.65 - 1.90, m, 2H; 1.55, m, 5H; 1.01 - 1.43, m, 6H; 0.80, m, 2H. MS (ESI(-)): 578 (M-H); (ESI(+)): 580. Calc'd for C₃₂H₄₁N₃O₃S₂: C 66.29, H 7.13, N 7.43: Found: C 65.82, H 7.03, N 7.34.

Example 995

N-[4-(1-ethylthio-4-phenylbut-2-oxymethyl)-2-(2-methylphenyl)benzoyl]methionine

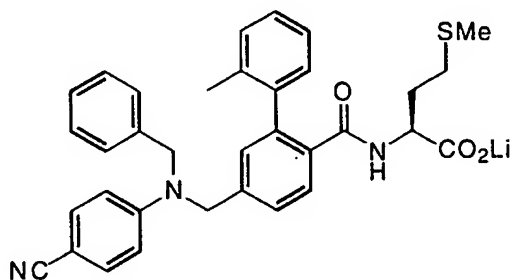
The desired compound was prepared according to the method of Example 158 ¹H (300MHz, CDCl₃, δ) 7.70 (1H, m), 7.38 (1H, dd, J=6&2Hz), 7.30-7.20 (6H, m), 7.20-7.05 (3H, m), 7.04 (1H, bs), 6.12 (1H, m), 6.00-5.40 (2H, m), 4.38 (1H, m), 4.01 (1H, m), 3.85 (1H, d, J=12Hz), 3.00-2.50 (5H, m), 2.37 (2H, m), 2.20-2.00 (6H, m), 1.98 (3H, s), 1.86 (2H, m), 1.57 (1H, m), 1.07 (3H, t, J=8Hz). m/e (ESI) 565 (MH⁺)
Anal.calc. for C₃₂H₄₀N₂O₃S₂·0.50 H₂O C 66.98, H 7.20, N 4.88 Found C 67.02, H 7.24, N 4.80

Example 996

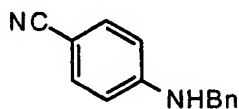
N-[4-(N-cyclohexylmethyl)-N-butananesulfonylamino]methyl-2-(2-methylphenyl)benzoyl]methionine

9485 The desired compound was prepared according to the method of Example 157 ¹H (300MHz, DMSO-d₆, δ) 7.54 (1H, m), 7.42 (1H, m), 7.30-7.10 (5H, m), 6.96 (1H, m), 4.40 (2H, m), 3.63 (1H, m), 3.08 (2H, m), 2.99 (2H, m), 2.17 (2H, m), 1.99 (2H, m), 1.90 (3H, s), 1.80-1.40 (10H, m), 1.37 (4H, m), 1.00 (2H, m), 1.87 (3H, t, J=8Hz), 1.73 (2H, m). m/e (ESI) 587 (MH⁺)

9490

Example 997

9495 N-[4-N-benzyl-N-(4-cyanophenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Example 997A

9500 A solution of 4-aminobenzonitrile (2.41 g, 20.0 mmol) and benzaldehyde (2.14 g, 20.0 mmol) in dichloroethane solvent (30 mL) was treated with Na(OAc)₃BH (6.69 g, 30.0 mmol) [CAUTION! - exothermic]. After 16 h the reaction mixture was carefully quenched by the addition of saturated aqueous NaHCO₃ (60 mL), and the resulting biphasic mixture was extracted with ethyl acetate (60 mL + 2 x 30 mL). The combined organic extracts were

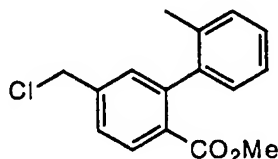
9505 rinsed with brine (30 mL), dried over MgSO₄, and concentrated under reduced pressure to provide an amber oil. Flash column chromatography eluting with hexane and ethyl acetate

using an elution gradient of 90:10 to 80:20 afforded 3.56 g of 997A as a white solid (86% yield).

^1H NMR (CDCl_3): δ 4.37 (d, $J = 5.4$ Hz, 2 H), 2.58-4.66 (br, 1 H), 6.58 (d, $J = 8.8$ Hz, 2

9510 H), 7.26-7.42 (comp, 7 H). LR

MS (CI^+): ($\text{M}+\text{H}$) $^+$ calc for $\text{C}_{14}\text{H}_{13}\text{N}_2$: 209; found: 209.



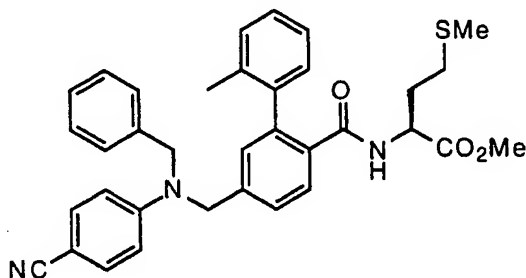
Example 997B

9515 A solution of 1178C (2.50 g, 9.75 mmol) and lithium chloride (0.537 g, 12.7 mmol) in dimethyl formamide solvent (10 mL) was treated dropwise with a solution of thionyl chloride (1.78 g, 14.6 mmol) in dimethyl formamide solvent (5 mL). After 15 h the reaction mixture was poured into water (125 mL), and the resulting solution was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were rinsed sequentially with

9520 water (2 x 20 mL), saturated aqueous sodium bicarbonate (3 x 20 mL), and then brine (20 mL). The organic portion was dried over MgSO_4 and concentrated under reduced pressure to provide a colorless oil. Flash column chromatography eluting with hexane and ethyl acetate using an elution gradient of 96:4 to 94:6 afforded 2.63 g of 997B as a colorless oil (98% yield).

9525 ^1H NMR (CDCl_3): δ 2.06 (s, 3 H), 3.61 (s, 3 H), 4.62 (s, 2 H), 7.07 (d, $J = 7.0$ Hz, 1 H), 7.17-7.31 (comp, 4 H), 7.45 (dd, $J = 1.5, 8.1$ Hz, 1 H), 7.97 (d, $J = 8.1$ Hz, 1 H). LR

MS (CI^+): ($\text{M}+\text{H}$) $^+$ calc for $\text{C}_{16}\text{H}_{15}\text{ClO}_2$: 274; found: 274; ($\text{M}+\text{NH}_4$) $^+$ calc for $\text{C}_{16}\text{H}_{18}\text{ClNO}_2$: 292; found: 292.



9530

Example 997C

A heterogeneous mixture of 997A (0.466 g, 2.0 mmol), 4-chloromethyl-2-(2-methylphenyl)benzoic acid, methyl ester, 997B (0.550 g, 2.00 mmol), K_2CO_3 (0.553 g, 4.00 mmol), and tetrabutylammonium iodide (0.0754 g, 0.200 mmol) in acetonitrile solvent

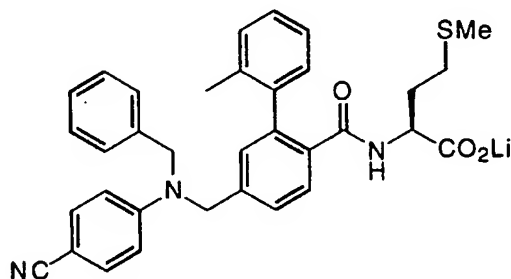
9535 (5 mL) was heated to 70 $^\circ\text{C}$. After 16 h the reaction mixture was returned to room

temperature, diluted with dimethylformamide (DMF) solvent (5 mL) and treated with solid LiOH (0.514 g, 12.0 mmol), and then heated to 90 °C for 10 h. The reaction mixture was returned to room temperature and diluted with additional DMF (10 mL). Triethylamine hydrochloride (1.40 g, 10.0 mmol) was added, followed by methionine methyl ester hydrochloride (0.807 g, 4.00 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOBT) (1.66 g, 10.0 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (1.96 g, 10.0 mmol). The mixture was heated to 60 °C for 18 h, cooled to room temperature, diluted with ethyl acetate (80 mL), and extracted with 2:1:1 H₂O: saturated aqueous NaHCO₃: brine (50 mL + 2 x 20 mL), followed by brine (10 mL). The organic layer was dried over MgSO₄, filtered through silica gel with 1:1 hexane: ethyl acetate rinses, and concentrated under reduced pressure to yield an amber oil. Radial chromatography eluting with hexane and ethyl acetate using an elution gradient of 80:20 to 50:50 afforded 0.0365 g of 997C as a colorless oil (3.2% yield).

¹H NMR (d₆-DMSO): δ 1.52-1.65 (m, 1 H), 1.79-1.91 (m, 1 H), 1.98-2.12 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.67 (m, 1 H), 4.72 (s, 2 H), 4.75 (s, 2 H), 5.81-5.90 (br, 1 H), 6.69 (d, J = 8.9 Hz, 2 H), 7.00 (d, J = 1.7 Hz, 1 H), 7.15-7.88 (comp, 10 H), 7.42 (d, J = 8.9 Hz, 2 H), 7.93 (dd, J = 8.1, 13.2 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₅H₃₆N₃O₃S: 578; found: 578. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₅H₃₄N₃O₃S: 576; found: 576.



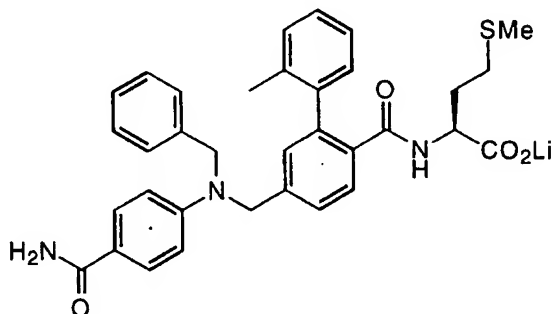
Example 997D

N-[4-N-benzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

A solution of 997C (0.0375 g, 0.0649 mmol) in methanol solvent (0.3 mL) was treated with LiOH (0.078 mL of a 1 M aqueous solution, 0.078 mmol) to afford a cloudy, white mixture which gradually became clear and colorless. After 8 h the reaction mixture was diluted with H₂O (2 mL) and extracted with diethyl ether (2 x 1 mL). The aqueous phase was lyophilized to provide 0.0332 g of 997D as a white solid (90% yield).

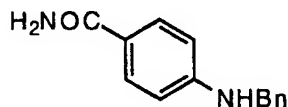
9565 ^1H NMR (d_6 -DMSO): δ 1.48-1.76 (comp, 2 H), 1.88-2.08 (comp, 8 H), 3.59-3.72 (br, 1 H), 4.83 (s, 2 H), 4.89 (s, 2 H), 6.76 (d, $J = 9.1$ Hz, 2 H), 6.90-6.96 (m, 1 H), 7.00 (s, 1 H), 7.07-7.37 (comp, 10 H), 7.47-7.53 (comp, 3 H). HR MS (FAB): $(\text{M}+\text{H})^+$ calc for $\text{C}_{34}\text{H}_{34}\text{N}_3\text{O}_3\text{S}$: 564.2321; found: 564.2325 (0.8 ppm error).

9570

Example 998

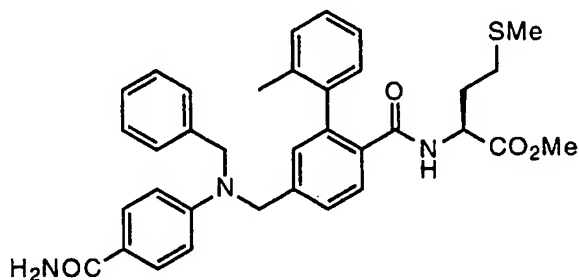
N-[4-N-benzyl-N-(4-carboxamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

9575

Example 998A

Compound 998A was prepared in the same fashion as 997A (69% yield).

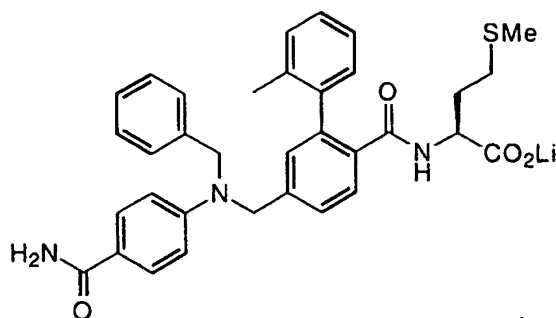
9580 ^1H NMR (d_6 -DMSO): δ 4.32 (d, $J = 5.9$ Hz, 2 H), 6.55 (d, $J = 8.6$ Hz, 2 H), 6.78-6.92 (br comp, 2 H), 7.20-7.26 (m, 1 H), 7.28-7.38 (comp, 4 H), 7.49-7.59 (br, 1 H), 7.60 (d, $J = 8.6$ Hz, 2 H). LR MS (CI $^+$): $(\text{M}+\text{H})^+$ calc for $\text{C}_{14}\text{H}_{15}\text{N}_2$: 227; found: 227.

Example 998B

Compound 998B was prepared in the same fashion as 997C (5.7% yield).

9585 ^1H NMR (d_6 -DMSO): δ 1.70-1.85 (comp, 2 H), 1.96 (s, 3 H), 1.97-2.24 (comp, 5 H), 3.58 (s, 3 H), 4.23-4.33 (br, 1 H), 4.80 (s, 2 H), 4.85 (s, 2 H), 6.68 (d, $J = 9.2$ Hz, 2

H), 6.86-6.94 (br, 1 H), 7.04-7.36 (comp, 14 H), 7.48 (d, J = 8.2 Hz, 1 H), 7.50-7.60 (br, 1 H), 7.63 (d, J = 8.8 Hz, 2 H), 8.30 (d, J = 7.8 Hz, 1 H): LR MS (ESI+): (M+H)⁺ calc for C₃₅H₃₈N₃O₄S: 596; found: 596. LR MS (ESI-): (M-H)⁻ calc for C₃₅H₃₆N₃O₄S: 594; found: 594.



9595

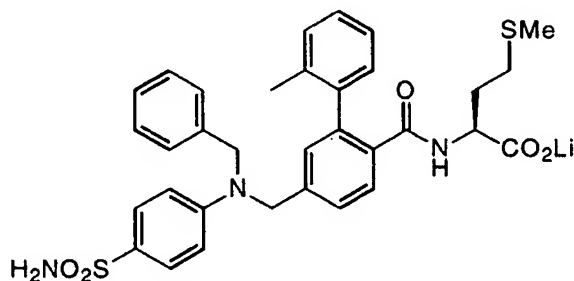
Example 998C

N-[4-N-benzyl-N-(4-carboxamidophenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 998C was prepared in the same fashion as 997D (100% yield).

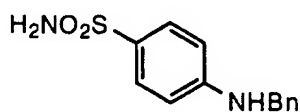
¹H NMR (d₆-DMSO): δ 1.47-1.61 (m, 1 H), 1.62-1.73 (m, 1 H), 1.87-2.08 (comp, 8 H), 3.59-3.70 (m, 1 H), 4.78 (s, 2 H), 6.67 (d, J = 8.9 Hz, 2 H), 6.86-6.94 (br comp, 2 H), 7.01 (s, 1 H), 7.05-7.35 (comp, 8 H), 7.50 (d, J = 7.8 Hz, 1 H), 7.54-7.61 (m, 1 H), 7.62 (d, J = 8.9 Hz, 1 H). HR MS (FAB): (M+Li)⁺ calc for C₃₄H₃₅LiN₃O₄S: 588.2508; found: 588.2502 (-1.0 ppm error).

9605

Example 999

N-[4-N-benzyl-N-(4-sulfonamidophenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

9610

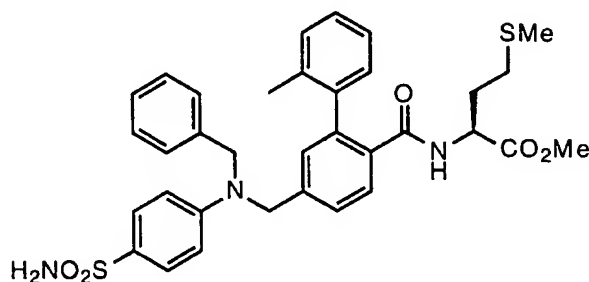


Example 999A

Compound 999A was prepared in the same fashion as 997A (51% yield).

9615 ^1H NMR (d_6 -DMSO): δ 4.34 (d, J = 6.3 Hz, 2 H), 6.63 (d, J = 8.8 Hz, 2 H), 6.90-6.94 (br, 2 H), 7.00-7.06 (m, 1 H), 7.20-7.26 (m, 1 H), 7.32-7.34 (comp, 4 H), 7.48 (d, J = 8.8 Hz, 2 H). LR

MS (CI $^+$): (M+H) $^+$ calc for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2\text{S}$: 263; found: 263.



9620

Example 999B

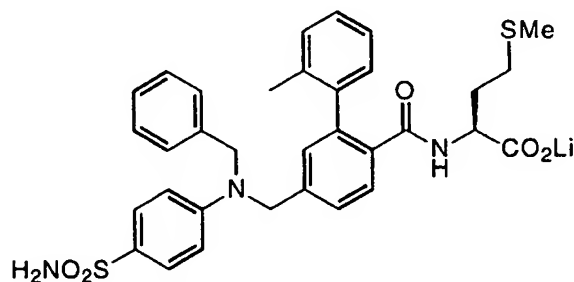
Compound 999B was prepared in the same fashion as 997C (1.3% yield).

9625 ^1H NMR (CDCl_3): δ 1.51-1.63 (m, 1 H), 1.78-1.91 (m, 1 H), 1.95-2.16 (comp, 8 H), 3.63 (app d, J = 4.0 Hz, 3 H), 4.14-4.20 (m, 2 H), 4.37 (d, J = 5.1 Hz, 2 H), 4.52-4.83 (comp, 3 H), 5.83-5.91 (m, 1 H), 6.59 (dd, J = 2.6, 8.8 Hz, 2 H), 7.07 (d, J = 8.1 Hz, 1 H), 7.24-7.40 (comp, 9 H), 7.61 (app t, J = 7.4 Hz, 2 H), 7.85 (dd, J = 7.8, 18.0 Hz, 1 H). LR

MS (ESI $^+$): (M+H) $^+$ calc for $\text{C}_{34}\text{H}_{38}\text{N}_3\text{O}_5\text{S}$: 632; found: 632. LR

MS (ESI $^-$): (M) $^-$ calc for $\text{C}_{34}\text{H}_{37}\text{N}_3\text{O}_5\text{S}$: 631; found: 631.

9630

Example 999C

N-[4-N-benzyl-N-(4-sulfonamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

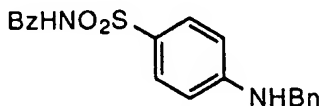
9635 Compound 999C was prepared in the same fashion as 997D (90% yield).

^1H NMR (d_6 -DMSO): δ 1.46-1.82 (comp, 2 H), 1.86-2.16 (comp, 8 H), 3.59-3.73 (m, 1 H), 3.99 (s, 2 H), 4.31 (app d, J = 5.9 Hz, 2 H), 6.55 (d, J = 8.0 Hz, 2 H), 6.74-7.37 (comp, 14 H), 7.72-7.80 (br, 1 H). HR

MS (FTMS): (M+H)⁺ calc for C₃₃H₃₆N₃O₃S₂: 618.2087; found: 618.2091 (-0.7 ppm error).

Example 1000

N-[4-N-benzyl-N-(4-N-benzoylsulfonamidophenyl)aminomethyl]-2-(2-methylphenyl)benzoylmethionine, lithium salt

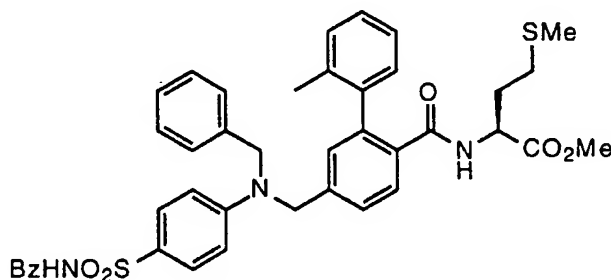


Example 1000A

Compound 1000A was prepared in the same fashion as 997A (81% yield).

¹H NMR (CDCl₃): δ 4.39 (d, J = 4.7 Hz, 2 H), 4.67-4.73 (br, 1 H), 6.62-6.67 (m, 2 H), 7.29-7.42 (comp, 5 H), 7.43-7.47 (comp, 2 H), 7.53-7.59 (m, 1 H), 7.74-7.79 (m, 2 H), 7.92-7.95 (m, 2 H), 8.46-8.80 (br, 1 H). LR

MS (CI⁺): (M+H)⁺ calc for C₂₀H₁₉N₂O₂S: 367; found: 367.



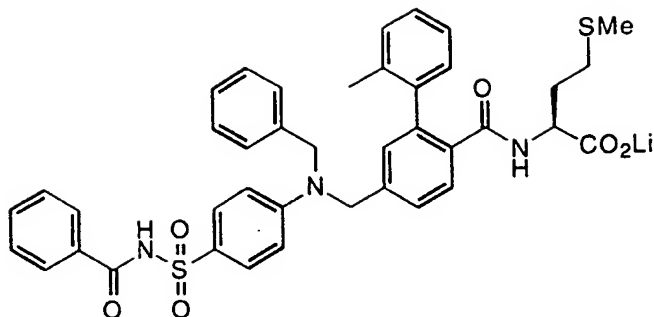
Example 1000B

Compound 1000B was prepared in the same fashion as 997C (5.6% yield).

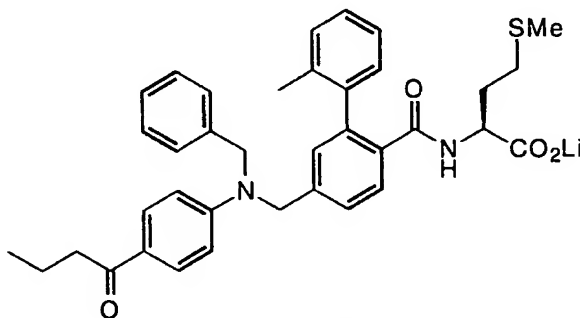
¹H NMR (CDCl₃): δ 1.52-1.66 (m, 1 H), 1.79-1.91 (m, 1 H), 1.99-2.10 (comp, 8 H), 3.65 (s, 3 H), 4.56-4.66 (m, 1 H), 4.72 (s, 2 H), 4.75 (s, 2 H), 5.86-5.93 (br, 1 H), 6.60-6.78 (comp, 2 H), 7.12-7.37 (comp, 9 H), 7.37-7.45 (comp, 3 H), 7.50-7.57 (m, 1 H), 7.87 (d, J = 7.8 Hz, 2 H), 7.86-7.94 (comp, 5 H), 8.02 (s, 1 H), 9.38 (s, 1 H), 10.70-10.86 (br, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₄₁H₄₂N₃O₆S: 736; found: 736. LR

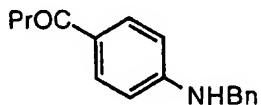
MS (ESI⁻): (M-H)⁻ calc for C₄₁H₄₀N₃O₆S: 734 found: 734.

Example 1000CN-[4-N-benzyl-N-(4-N-benzoylsulfonamidophenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

- 9670 Compound 1000C was prepared in the same fashion as 997D (77% yield).
¹H NMR (d₆-DMSO): δ 1.48-1.76 (comp, 2 H), 1.89-2.06 (comp, 8 H), 3.67-3.77 (br, 1 H), 4.29 (d, J = 5.9 Hz, 1 H), 4.74 (s, 2 H), 4.79 (s, 2 H), 6.49 (d, J = 8.9 Hz, 1 H), 6.60-6.66 (m, 2 H), 6.95-7.35 (comp, 15 H), 7.47-7.58 (comp, 2 H), 7.86 (d, J = 7.2 Hz, 2 H). LR
 9675 MS (ESI⁻): (M-H)⁻ calc for C₄₀H₃₈N₃O₆S₂: 720; found: 720.

Example 1001N-[4-N-benzyl-N-(4-propionylphenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

9680

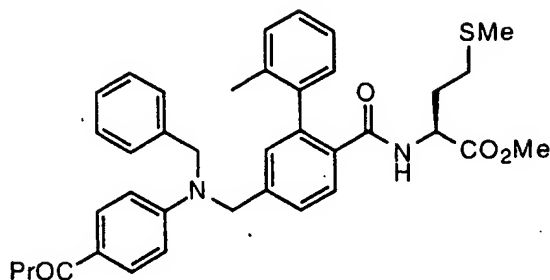
Example 1001A

9685

- Compound 1001A was prepared in the same fashion as 997A (89% yield).
¹H NMR (CDCl₃): δ 0.97 (t, J = 7.4 Hz, 3 H), 1.73 (tq, J = 7.3, 7.4 Hz, 2 H), 2.82 (t, J = 7.3 Hz, 2 H), 4.39 (d, J = 4.0 Hz, 2 H), 4.56-4.63 (br, 1 H), 6.59 (d, J = 9.0 Hz, 2 H), 7.25-7.35 (comp, 5 H), 7.82 (d, J = 9.0 Hz, 2 H). LR

MS (CI⁺): (M+H)⁺ calc for C₁₇H₂₀NO: 254; found: 254.

9690



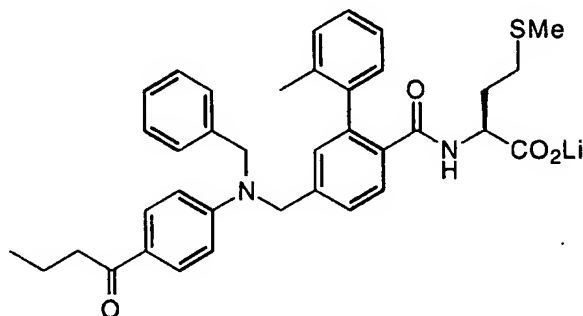
Example 1001B

Compound 1001B was prepared in the same fashion as 997C (49% yield).

¹H NMR (CDCl₃): δ 0.97 (t, J = 7.5 Hz, 3 H), 1.52-1.66 (m, 1 H), 1.73 (app q, J = 7.5 Hz, 2 H), 1.78-1.91 (m, 1 H), 1.99-2.13 (comp, 8 H), 2.82 (t, J = 7.5 Hz, 2 H), 3.66 (s, 3 H), 4.53-4.67 (m, 1 H), 4.73 (s, 2 H), 4.76 (s, 2 H), 5.84-5.90 (m, 1 H), 6.71 (d, J = 8.9 Hz, 2 H), 7.04 (d, J = 1.7 Hz, 1 H), 7.14-7.37 (comp, 10 H), 7.82 (d, J = 8.9 Hz, 2 H), 7.92 (dd, J = 8.1, 13.2 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₈H₄₃N₂O₄S: 623; found: 623. LR

MS (ESI⁻): (M-H)⁻ calc for C₂₈H₄₁N₂O₄S: 621; found: 621.



Example 1001C

N-[4-N-benzyl-N-(4-propionylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

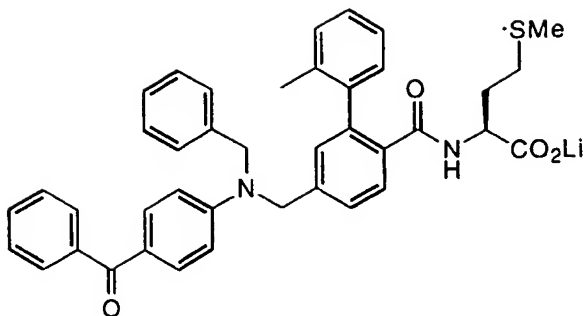
9705

Compound 1001C was prepared in the same fashion as 997D (98% yield).

¹H NMR (d₆-DMSO): δ 0.88 (t, J = 7.3 Hz, 3 H), 1.50-1.63 (comp, 3 H), 1.63-1.78 (m, 1 H), 1.79-2.11 (comp, 8 H), 2.78 (t, J = 7.3 Hz, 2 H), 3.72-3.81 (br, 1 H), 4.82 (s, 2 H), 4.87 (s, 2 H), 6.74 (d, J = 9.2 Hz, 2 H), 6.94-7.02 (br, 1 H), 7.02 (s, 1 H), 7.09-7.36 (comp, 10 H), 7.52 (d, J = 7.8 Hz, 1 H), 7.73 (d, J = 9.2 Hz, 2 H). HR

9710

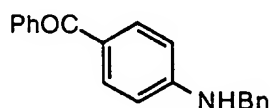
MS (FAB): (M+2Li-H)⁺ calc for C₃₇H₃₉Li₂N₂O₄S: 621.2951; found: 621.2966 (2.4 ppm error).



9715

Example 1002

N-[4-N-benzyl-N-(4-benzoylphenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine,
lithium salt



9720

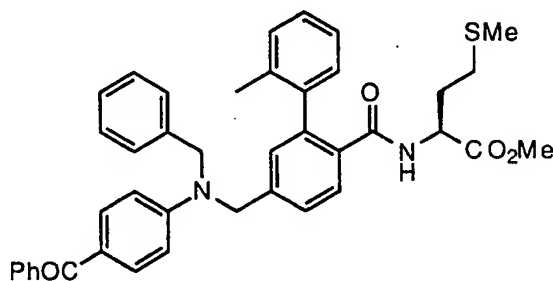
Example 1002A

Compound 1002A was prepared in the same fashion as 997A (63% yield).

^1H NMR (d_6 -DMSO): δ 3.37 (s, 1 H), 4.38 (d, J = 6.2 Hz, 2 H), 6.68 (d, J = 8.8 Hz, 2 H), 7.22-7.28 (m, 1 H), 7.31-7.38 (comp, 4 H), 7.46-7.62 (comp, 7 H). LR

9725 MS (ESI $^{+}$): (M+H) $^{+}$ calc for $\text{C}_{20}\text{H}_{18}\text{NO}$: 288; found: 288. LR

MS (ESI $^{-}$): (M-H) $^{-}$ calc for $\text{C}_{20}\text{H}_{16}\text{NO}$: 286; found: 286.

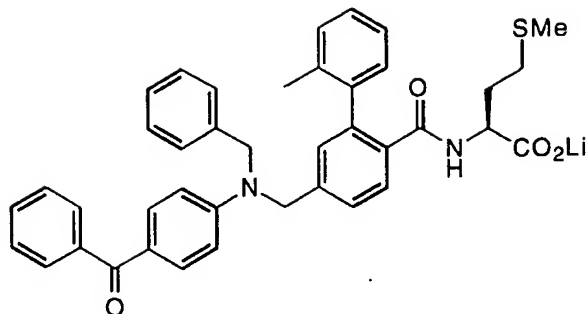
Example 1002B

9730 Compound 1002B was prepared in the same fashion as 997C (30% yield).

^1H NMR (CDCl_3): δ 1.52-1.68 (m, 1 H), 1.79-1.93 (m, 1 H), 1.98-2.16 (comp, 8 H), 3.67 (s, 3 H), 4.56-4.70 (m, 1 H), 4.76 (s, 2 H), 4.78 (s, 2 H), 5.85-5.92 (m, 1 H), 6.74 (d, J = 9.2 Hz, 2 H), 7.05 (s, 1 H), 7.14-7.38 (comp, 10 H), 7.40-7.48 (comp, 2 H), 7.69-7.78 (comp, 4 H), 7.94 (dd, J = 8.1, 13.3 Hz, 1 H). LR

9735 MS (ESI $^{+}$): (M+H) $^{+}$ calc for $\text{C}_{41}\text{H}_{41}\text{N}_2\text{O}_4\text{S}$: 657; found: 657. LR

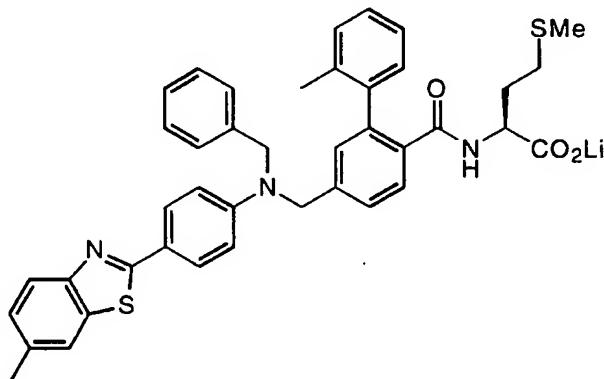
MS (ESI $^{-}$): (M-H) $^{-}$ calc for $\text{C}_{41}\text{H}_{39}\text{N}_2\text{O}_4\text{S}$: 655; found: 655.

Example 1002C

9740 N-[4-N-benzyl-N-(4-benzoylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
lithium salt

Compound 1002C was prepared in the same fashion as 997D (86% yield).

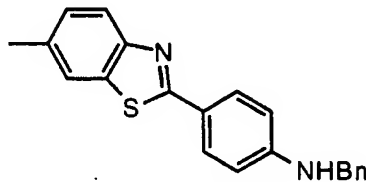
¹H NMR (d₆-DMSO): δ 1.49-1.63 (m, 1 H), 1.63-1.77 (m, 1 H), 1.78-2.10 (comp, 8 H),
 3.68-3.76 (br, 1 H), 4.84 (s, 2 H), 4.89 (s, 2 H), 6.81 (d, J = 9.1 Hz, 2 H), 6.96 (d, J =
 9745 5.4 Hz, 1 H), 7.03 (s, 1 H), 7.08-7.37 (comp, 11 H), 7.46-7.61 (comp, 7 H). HR
 MS (FAB): (M+Li)⁺ calc for C₄₀H₃₈LiN₂O₄S: 649.2712; found: 649.2723 (1.6 ppm
 error).



9750

Example 1003

N-[4-N-benzyl-N-(4-(6-methylbenzothiazol-2-yl)phenyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine, lithium salt



9755

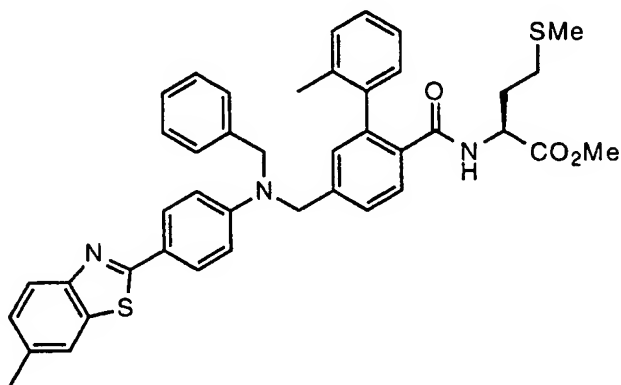
Example 1003A

Compound 1003A was prepared in the same fashion as 997A (38% yield).

^1H NMR (CDCl_3): δ 2.47 (s, 3 H), 4.41 (app s, 3 H), 6.65-6.70 (m, 2 H), 7.22-7.38 (comp, 6 H), 7.62 (s, 1 H), 7.83-7.91 (comp, 3 H). LR

MS (ESI+): (M+H)⁺ calc for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{S}$: 330; found: 330. LR

MS (ESI-): (M-H)⁻ calc for $\text{C}_{21}\text{H}_{17}\text{N}_2\text{S}$: 329; found: 329.



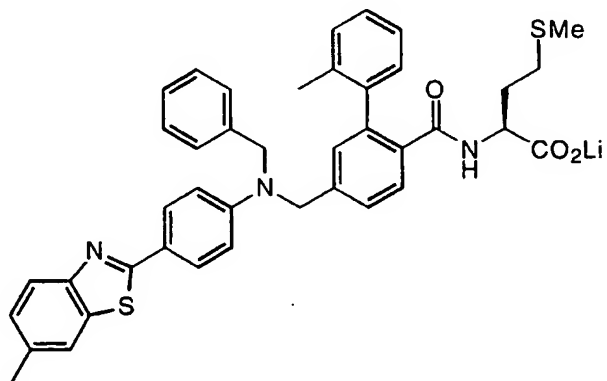
Example 1003B

Compound 1003B was prepared in the same fashion as 997C (16% yield).

^1H NMR (CDCl_3): δ 1.52-1.72 (br m, 1 H), 1.80-1.92 (m, 1 H), 1.99-2.14 (comp, 8 H), 2.48 (s, 2 H), 3.66 (s, 3 H), 4.56-4.68 (m, 1 H), 4.74 (s, 2 H), 4.77 (s, 2 H), 5.84-5.90 (m, 1 H), 6.79 (d, J = 8.8 Hz, 2 H), 7.07 (s, 1 H), 7.24-7.38 (comp, 11 H), 7.62 (s, 2 H), 7.85-7.98 (comp, 4 H). LR

MS (ESI+): (M+H)⁺ calc for $\text{C}_{42}\text{H}_{42}\text{N}_3\text{O}_3\text{S}_2$: 698; found: 698. LR

MS (ESI-): (M-H)⁻ calc for $\text{C}_{42}\text{H}_{40}\text{N}_3\text{O}_3\text{S}_2$: 700; found: 700.

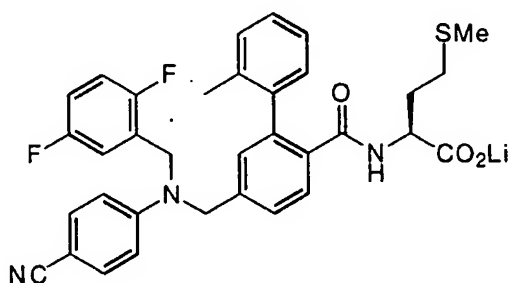


Example 1003C

N-[4-N-benzyl-N-(4-(6-methylbenzthiazol-2-yl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

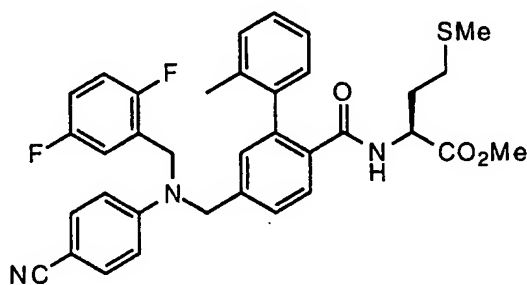
Compound 1003C was prepared in the same fashion as 997D (93% yield).

¹H NMR (d₆-DMSO): δ 1.48-1.62 (m, 1 H), 1.62-1.73 (m, 1 H), 1.80-2.11 (comp, 8 H), 2.41 (s, 3 H), 3.64-3.73 (br, 1 H), 4.82 (s, 2 H), 4.87 (s, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 6.95 (d, J = 5.8 Hz, 1 H), 7.04 (s, 1 H), 7.08-7.37 (comp, 11 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.76-7.82 (comp, 4 H). HR MS (FAB): (M⁺)⁺ calc for C₄₁H₃₈N₃O₃S₂: 685.2433; found: 685.2421 (-1.8 ppm error).



Example 1004

N-[4-N-2,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt



Example 1004A

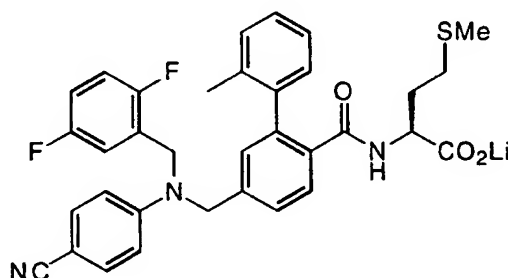
A heterogeneous mixture of 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) (0.638 g, 2.00 mmol), 4-aminobenzonitrile (0.241 g, 2.0 mmol), K₂CO₃ (1.11 g, 8.00 mmol), and tetrabutylammonium iodide (0.0754 g, 0.200 mmol) in acetonitrile solvent (5 mL) was heated to 70 °C for 18 h. Next, 2,5-difluorobenzyl bromide (0.507 g, 2.40 mmol) was added, and the reaction mixture was returned to 70 °C. After 16 h the reaction mixture was cooled to room temperature, diluted with DMF solvent (5 mL) and treated with solid LiOH (0.514 g, 12.0 mmol), and then heated to 90 °C for 14 h. The reaction mixture was cooled to room temperature and diluted with additional DMF (20 mL). Triethylamine hydrochloride (1.40 g, 10.0 mmol) was added, followed by methionine methyl ester hydrochloride (0.807 g, 4.00 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOBT) (1.66 g, 10.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (1.96 g, 10.0 mmol), and finally, triethylamine (1.02 g, 10.0 mmol). The mixture was

heated to 60 °C for 8 h, cooled to room temperature, diluted with ethyl acetate (80 mL), and
 9805 extracted with 2:1:1 H₂O: saturated aqueous NaHCO₃: brine (50 mL + 2 x 20 mL),
 followed by brine (10 mL). The organic layer was dried over MgSO₄, filtered through silica
 gel with 1:1 hexane: ethyl acetate rinses, and concentrated under reduced pressure to yield
 an amber oil. Radial chromatography eluting with hexane and ethyl acetate using an elution
 gradient of 70:30 to 50:50 afforded 0.142 g of 1004A as a colorless oil (12% yield).

9810 ¹H NMR (CDCl₃): δ 1.53-1.66 (m, 1 H), 1.80-1.92 (m, 1 H), 1.98-2.12 (comp, 8 H),
 3.66 (s, 3 H), 4.56-4.67 (m, 1 H), 4.71 (s, 2 H), 4.75 (s, 2 H), 5.86-5.96 (m, 1 H), 6.69
 (d, J = 9.0 Hz, 2 H), 6.78-6.89 (comp, 2 H), 7.00 (s, 1 H), 7.04-7.37 (comp, 6 H), 7.44
 (d, J = 9.0 Hz, 2 H), 7.93 (dd, J = 8.1, 13.5 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₅H₃₄F₂N₃O₃S: 614; found: 614. LR

9815 MS (ESI⁻): (M-H)⁻ calc for C₃₅H₃₂F₂N₃O₃S: 612; found: 612.



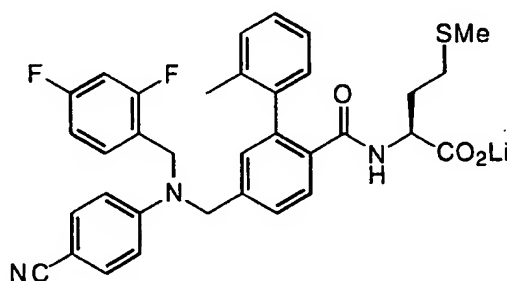
Example 1004B

N-[4-N-2,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)
 9820 benzoyl]methionine, lithium salt

Compound 1004B was prepared in the same fashion as 997D (93% yield).

¹H NMR (d₆-DMSO): δ 1.50-1.80 (comp, 2 H), 1.90-2.12 (comp, 8 H), 3.64-3.81 (m, 1
 H), 4.84-5.00 (comp, 4 H), 6.75-6.88 (comp, 2 H), 6.89-7.08 (comp, 3 H), 7.11-7.40
 (comp, 6 H), 7.48-7.63 (comp, 3 H). HR

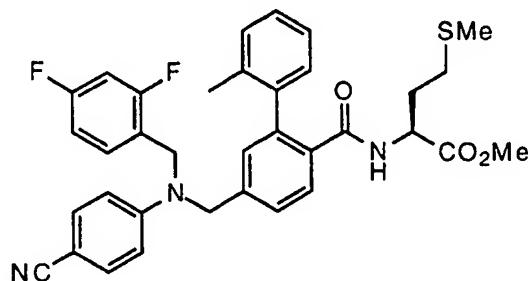
9825 MS (FAB): (M+H)⁺ calc for C₃₄H₃₂F₂N₃O₃S: 600.2132; found: 600.2139 (1.1 ppm
 error).



9830

Example 1005

N-[4-N-2,4-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt



9835

Example 1005A

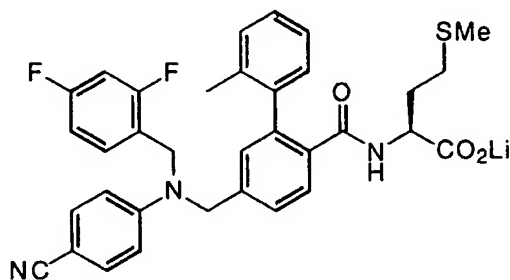
Compound 1005A was prepared starting from 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) in the same fashion as 1004A (14% yield).

¹H NMR (CDCl₃): δ 1.53-1.66 (m, 1 H), 1.80-1.92 (m, 1 H), 1.98-2.12 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.67 (m, 1 H), 4.71 (s, 2 H), 4.75 (s, 2 H), 5.86-5.92 (m, 1 H), 6.69 (d, J = 9.0 Hz, 2 H), 6.79-6.89 (comp, 2 H), 7.00 (s, 1 H), 7.04-7.37 (comp, 6 H), 7.44 (d, J = 9.0 Hz, 2 H), 7.93 (dd, J = 8.1, 13.5 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₅H₃₄F₂N₃O₃S: 614; found: 614. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₅H₃₂F₂N₃O₃S: 612; found: 612.

9845

Example 1005B

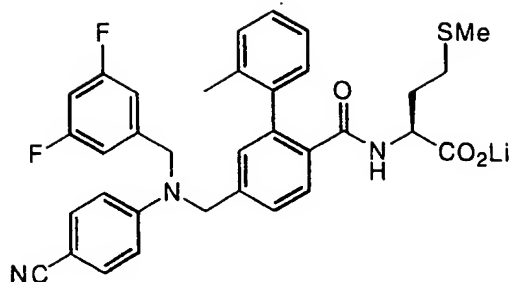
N-[4-N-2,4-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1005B was prepared in the same fashion as 997D (80% yield).

¹H NMR (d₆-DMSO): δ 1.48-1.62 (m, 1 H), 1.62-1.73 (m, 1 H), 1.89-2.07 (comp, 8 H), 3.62-3.72 (br, 1 H), 4.82-4.88 (comp, 4 H), 6.79 (d, J = 9.1 Hz, 2 H), 6.90-7.32 (comp, 10 H), 7.48-7.54 (comp, 3 H). HR

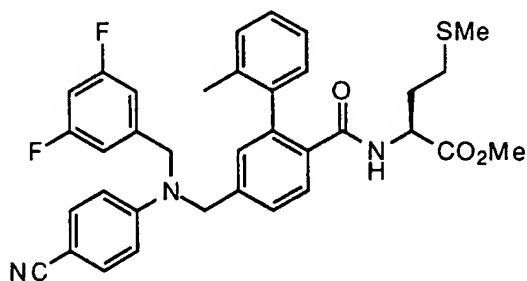
MS (FAB): (M+H)⁺ calc for C₃₄H₃₂F₂N₃O₃S: 600.2132; found: 600.2144 (2.0 ppm

error).

Example 1006

9860

N-[4-N-(3,5-difluorobenzyl)-N-(4-cyanophenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Example 1006A

9865

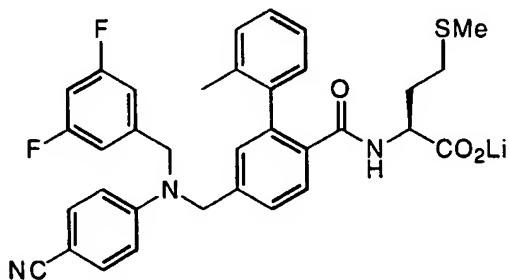
Compound 1006A was prepared starting from 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) in the same fashion as 1004A (28% yield).

¹H NMR (CDCl₃): δ 1.53-1.65 (m, 1 H), 1.80-1.91 (m, 1 H), 1.98-2.12 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.66 (m, 1 H), 4.67 (s, 2 H), 4.76 (s, 2 H), 5.88 (d, J = 7.2 Hz, 1 H), 6.64-6.76 (comp, 5 H), 7.00 (d, J = 1.3 Hz, 1 H), 7.13-7.36 (comp, 5 H), 7.44 (d, J = 8.8 Hz, 2 H), 7.94 (dd, J = 8.1, 13.2 Hz, 1 H). LR

9870

MS (ESI⁺): (M+H)⁺ calc for C₃₅H₃₄F₂N₃O₃S: 614; found: 614. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₅H₃₂F₂N₃O₃S: 612; found: 612.



9875

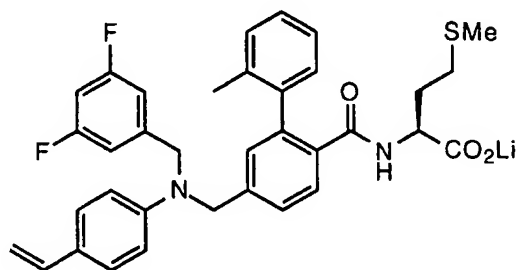
Example 1006B

N-[4-N-3,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1006B was prepared in the same fashion as 997D (82% yield).

9880 ^1H NMR (d_6 -DMSO): δ 1.48-1.75 (comp, 2 H), 1.90-2.07 (comp, 8 H), 3.66-3.76 (br, 1 H), 4.86 (s, 2 H), 4.92 (s, 2 H), 6.76 (d, J = 8.8 Hz, 2 H), 6.92-7.00 (comp, 4 H), 7.07-7.24 (comp, 5 H), 7.30 (dd, J = 1.5, 8.12 Hz, 1 H), 7.50-7.55 (comp, 3 H). HR MS (FAB): $(\text{M}+\text{H})^+$ calc for $\text{C}_{34}\text{H}_{32}\text{F}_2\text{N}_3\text{O}_3\text{S}$: 600.2132; found: 600.2140 (1.2 ppm error).

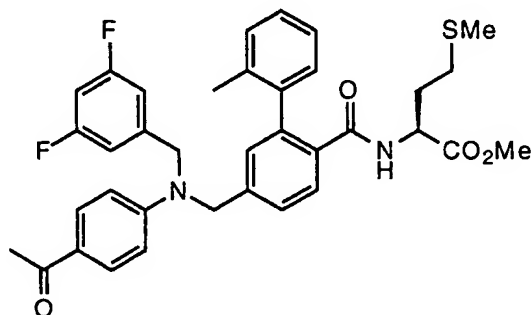
9885



Example 1007

N-[4-N-3,5-difluorobenzyl-N-(4-vinylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

9890



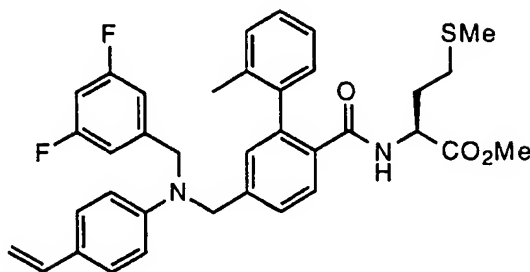
Example 1007A

Compound 1007A was prepared starting from 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) in the same fashion as 1004A (11% yield).

9895 ^1H NMR (CDCl_3): δ 1.52-1.65 (m, 1 H), 1.80-1.91 (m, 1 H), 1.95-2.12 (comp, 8 H), 2.50 (s, 3 H), 3.67 (s, 3 H), 4.56-4.67 (m, 1 H), 4.70 (s, 2 H), 4.78 (s, 2 H), 5.89 (dd, J = 2.5, 7.7 Hz; 1 H), 6.65-6.77 (comp, 5 H), 7.04 (s, 1 H), 7.13-7.36 (comp, 5 H), 7.83 (d, J = 9.2 Hz, 2 H), 7.94 (dd, J = 8.1, 13.8 Hz, 1 H). LR MS (ESI+): $(\text{M}+\text{H})^+$ calc for $\text{C}_{36}\text{H}_{37}\text{F}_2\text{N}_2\text{O}_4\text{S}$: 631; found: 631. LR

9900

MS (ESI-): (M-H)⁻ calc for C₃₆H₃₅F₂N₂O₄S: 629; found: 629.



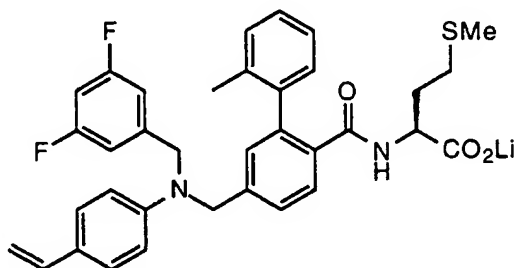
Example 1007B

A solution of 1007A (0.147 g, 0.233 mmol) in 1:1 tetrahydrofuran: methanol solvent (2 mL) was treated with NaBH₄ (0.0315 g, 0.815 mmol). After 1 h the mixture was quenched by the addition of H₂O (2 mL), followed by a few drops of 3 M HCl. The reaction mixture was then extracted with ethyl acetate (4 x 2 mL), and the combined organic extracts were rinsed with brine (1 mL), dried over MgSO₄, filtered through silica gel with ethyl acetate rinses, and concentrated under reduced pressure to afford an amber oil. Radial chromatography eluting with hexane and ethyl acetate using an elution gradient of 60:40 to 30:70 afforded 0.0097 g of 1007B as a colorless oil (6.8% yield).

¹H NMR (CDCl₃): δ 1.52-1.62 (comp, 2 H), 1.80-1.91 (m, 1 H), 1.99-2.14 (comp, 8 H), 3.66 (s, 3 H), 4.58-4.66 (comp, 3 H), 4.70 (s, 2 H), 5.04 (d, J = 11.1 Hz, 1 H), 5.53 (d, J = 17.6 Hz, 1 H), 5.84-5.90 (m, 1 H), 6.55-6.67 (comp, 3 H), 6.67-6.79 (comp, 2 H), 7.05 (s, 1 H), 7.23-7.34 (comp, 8 H), 7.92 (dd, J = 8.1, 13.6 Hz, 1 H). LR

MS (ESI+): (M+H)⁺ calc for C₃₆H₃₇F₂N₂O₃S: 615; found: 615. LR

MS (ESI-): (M-H)⁻ calc for C₃₆H₃₅F₂N₂O₃S: 613; found: 613.

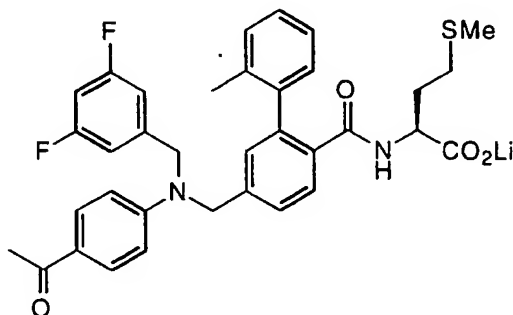


Example 1007C

N-[4-N-3,5-difluorobenzyl-N-(4-vinylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1007C was prepared in the same fashion as 997D (72% yield).
¹H NMR (d₆-DMSO): δ 1.60-1.70 (br m, 1 H), 1.70-1.83 (br m, 1 H), 1.88-2.06 (br comp, 8 H), 3.58-3.68 (br, 1 H), 4.65-4.77 (br comp, 1 H), 4.75 (s, 2 H), 4.81 (s, 2 H),

4.96 (d, J = 11.0 Hz, 1 H), 5.51 (dd, J = 1.2, 17.7 Hz, 1 H), 6.54 (dd, J = 11.0, 17.7 Hz, 1 H), 6.65 (d, J = 9.2 Hz, 2 H), 6.89-7.00 (comp, 4 H), 7.01-7.22 (comp, 4 H), 7.23 (d, J = 9.2 Hz, 2 H), 7.30-7.33 (m, 1 H), 7.51 (d, J = 7.9 Hz, 1 H). LR MS (ESI⁻): (M-H)⁻ calc for C₃₅H₃₂F₂LiN₃O₃S: 599; found: 599.



9935

1008

N-[4-N-3,5-difluorobenzyl-N-(4-acetylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

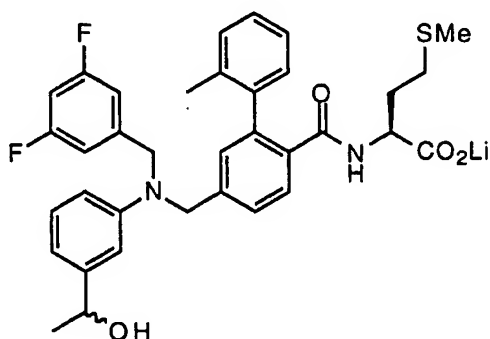
Compound 1008 was prepared in the same fashion as 997D (86% yield).

¹H NMR (d₆-DMSO): δ 1.46-1.61 (m, 1 H), 1.61-1.73 (m, 1 H), 1.86-2.08 (comp, 8 H), 2.38 (s, 3 H), 3.58-3.68 (br, 1 H), 4.85 (s, 2 H), 4.90 (s, 2 H), 6.73 (d, J = 9.0 Hz, 2 H), 6.90-7.00 (comp, 5 H), 7.05-7.20 (comp, 5 H), 7.30 (dd, J = 1.7, 7.8 Hz, 1 H), 7.52 (d, J = 7.8 Hz, 1 H), 7.74 (d, 9.0 Hz, 2 H). HR

9940

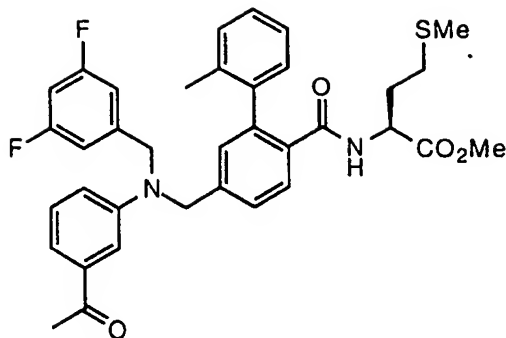
MS (FAB): (M+H)⁺ calc for C₃₅H₃₅F₂N₂O₄S: 617.2286; found: 617.2277 (-1.5 ppm error).

9945

Example 1009

N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

9950

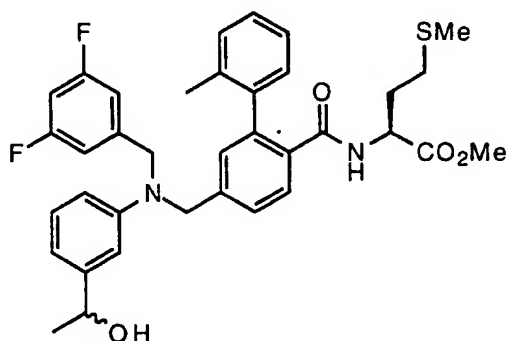
Example 1009A

Compound 1009A was prepared starting from 4-chloromethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 997B) in the same fashion as 1004A (17% yield).

¹H NMR (CDCl₃): δ 1.52-1.65 (m, 1 H), 1.79-1.91 (m, 1 H), 2.00-2.14 (comp, 8 H), 2.52 (s, 3 H), 2.67 (s, 3 H), 4.56-4.66 (m, 1 H), 4.66 (s, 2 H), 4.74 (s, 2 H), 5.85-5.91 (m, 1 H), 6.64-6.81 (comp, 3 H), 6.86 (d, J = 8.1 Hz, 1 H), 7.05 (s, 1 H), 7.14-7.35 (comp, 8 H), 7.92 (dd, J = 8.1, 14.0 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₆H₃₇F₂N₂O₄S: 631; found: 631. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₆H₃₅F₂N₂O₄S: 629; found: 629.

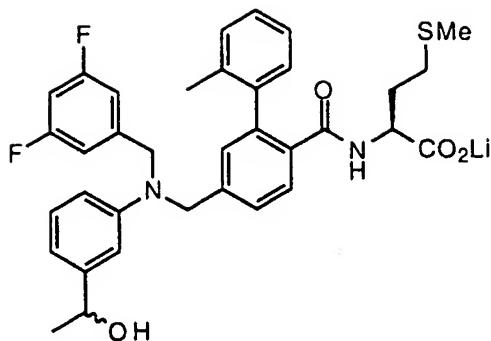
Example 1009B

Compound 1009B was prepared in the same fashion as 1007B (10% yield).

¹H NMR (CDCl₃): δ 1.41 (d, J = 6.5 Hz, 3 H), 1.52-1.65 (comp, 2 H), 1.77 (d, J = 2.7 Hz, 1 H), 1.79-1.91 (m, 1 H), 1.99-2.15 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.65 (comp, 3 H), 4.69 (s, 2 H), 4.73-4.82 (m, 1 H), 5.85-5.91 (m, 1 H), 6.59 (dd, J = 2.4, 8.2 Hz, 1 H), 6.64-6.80 (comp, 5 H), 7.06 (d, J = 1.3 Hz, 1 H), 7.15-7.19 (m, 1 H), 7.21-7.36 (comp, 5 H), 7.92 (dd, J = 8.1, 14.3 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₆H₃₉F₂N₂O₄S: 633; found: 633. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₆H₃₇F₂N₂O₄S: 631; found: 631.



9975

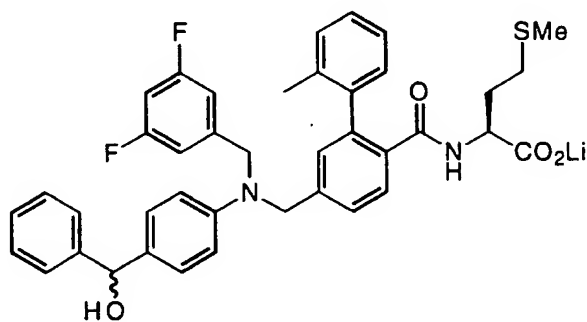
Example 1009C

N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1009C was prepared in the same fashion as 997D (76% yield).

9980 ^1H NMR (d_6 -DMSO): δ 1.18 (d, $J = 6.1$ Hz, 3 H), 1.47-1.60 (m, 1 H), 1.60-1.73 (m, 1 H), 1.88-2.09 (comp, 8 H), 3.59-3.68 (m, 1 H), 4.89-4.57 (m, 1 H), 4.71 (s, 2 H), 4.78 (s, 2 H), 4.99 (d, $J = 4.1$ Hz, 1 H), 6.50 (dd, $J = 2.3, 8.4$ Hz, 1 H), 6.61 (d, $J = 7.4$ Hz, 1 H), 6.70 (s, 1 H), 6.89-7.03 (comp, 4 H), 7.03-7.21 (dd, $J = 1.3, 7.8$ Hz, 1 H), 7.51 (d, $J = 9.8$ Hz, 1 H). HR

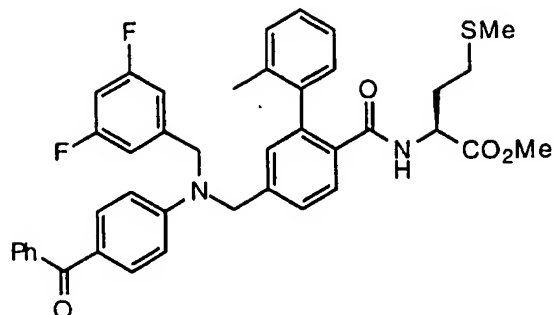
9985 MS (FAB): $(\text{M}+\text{H})^+$ calc for $\text{C}_{35}\text{H}_{36}\text{F}_2\text{N}_3\text{O}_4\text{S}$: 618.2364; found: 618.2366 (0.4 ppm error).



9990

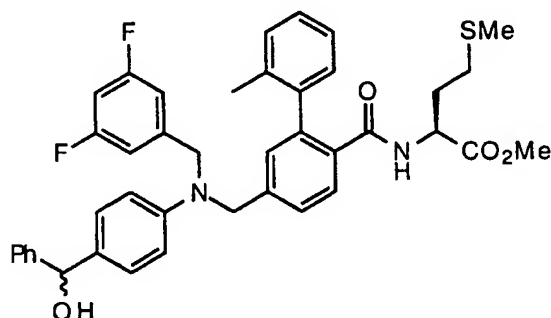
Example 1010

N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxy-1-phenylmethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Example 1010A

Compound 1010A was prepared starting from 4-chloromethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 997B) in the same fashion as 1004A (5.4% yield).

^1H NMR (CDCl_3): δ 1.53-1.66 (m, 1 H), 1.80-1.91 (m, 1 H), 2.00-2.13 (comp, 8 H), 3.66 (s, 3 H), 4.55-4.66 (m, 1 H), 4.71 (s, 2 H), 4.79 (s, 2 H), 5.86-5.92 (m, 1 H), 6.68-6.78 (comp, 5 H), 7.05 (d, $J = 1.6$ Hz, 1 H), 7.14-7.35 (comp, 6 H), 7.40-7.47 (comp, 2 H), 7.49-7.55 (m, 1 H), 7.70-7.77 (comp, 4 H), 7.94 (dd, $J = 8.2, 13.3$ Hz, 1 H). LR MS (ESI $^-$): (M-H) $^-$ calc for $\text{C}_{41}\text{H}_{37}\text{F}_2\text{N}_2\text{O}_4\text{S}$: 691; found: 691.

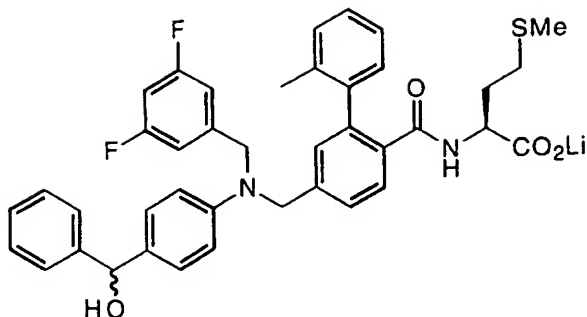
Example 1010B

Compound 1010B was prepared in the same fashion as 1007B (6.5% yield).

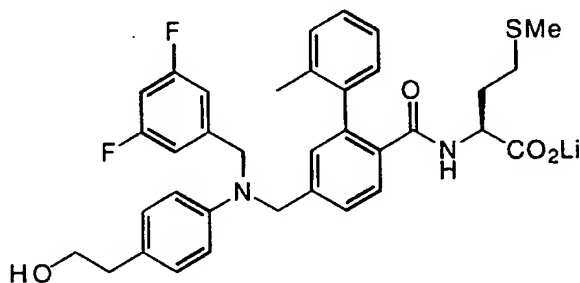
^1H NMR (CDCl_3): δ 1.52-1.64 (comp, 2 H), 1.78-1.91 (m, 1 H), 1.99-2.11 (comp, 8 H), 3.66 (s, 3 H), 4.55-4.65 (comp, 3 H), 4.68 (s, 2 H), 5.70 (d, $J = 2.9$ Hz, 1 H), 5.86 (t, $J = 6.4$ Hz, 1 H), 6.63 (d, $J = 8.5$ Hz, 2 H), 6.67-6.72 (m, 1 H), 6.75 (d, $J = 6.2$ Hz, 2 H), 7.04 (s, 1 H), 7.17 (d, $J = 8.5$ Hz, 2 H), 7.19-7.41 (comp, 10 H), 7.91 (dd, $J = 8.0, 21.3$ Hz, 1 H). LR

MS (ESI $^+$): (M-OH) $^+$ calc for $\text{C}_{41}\text{H}_{39}\text{F}_2\text{N}_2\text{O}_3\text{S}$: 677; found: 677. LR

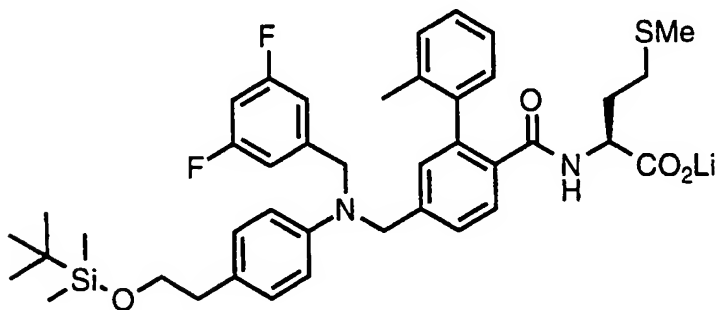
MS (ESI $^-$): (M-H) $^-$ calc for $\text{C}_{41}\text{H}_{39}\text{F}_2\text{N}_2\text{O}_4\text{S}$: 693; found: 693.

Example 1010CN-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxy-1-phenylmethyl)phenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

- 10020 Compound 1010C was prepared in the same fashion as 997D (100% yield).
¹H NMR (d₆-DMSO): δ 1.50-1.59 (br m, 1 H), 1.62-1.70 (br m, 1 H), 1.88-2.23 (br comp, 8 H), 4.68 (s, 2 H), 4.77 (s, 2 H), 6.66 (d, J = 8.5 Hz, 2 H), 6.92-6.95 (comp, 3 H), 7.02-7.07 (comp, 3 H), 7.11-7.26 (comp, 5 H), 7.27-7.32 (comp, 5 H), 7.49 (d, J = 8.0 Hz, 1 H). LR
 10025 MS (ESI⁻): (M-H)⁻ calc for C₄₀H₃₇F₂LiN₂O₄S: 678; found: 678.

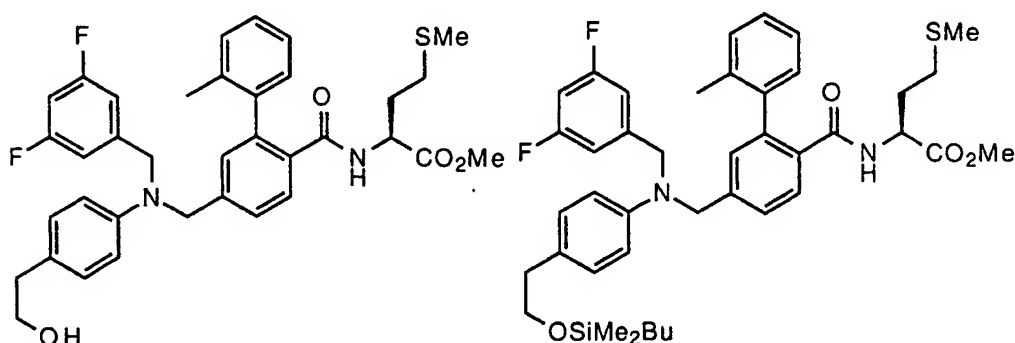
Example 1011

- 10030 N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Example 1012

10035

N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl]-
2-(2-methylphenyl)benzoyl]methionine, lithium salt



Example 1011A and Example 1012A

10040

Compound 1012A was prepared starting from 4-chloromethyl-2-(2-methylphenyl)benzoic acid, methyl ester, 997B, in the same fashion as 1004A (4.1% yield). Compound 1011A was isolated from the crude reaction mixture as a side-product (15% yield).

¹H NMR (CDCl₃): δ 1.44-1.50 (br, 1 H), 1.52-1.65 (m, 1 H), 1.80-1.91 (m, 1 H), 1.99-2.12 (comp, 8 H), 2.76 (t, J = 6.4 Hz, 2 H), 3.66 (s, 3 H), 3.80 (br t, J = 6.4 Hz, 2 H), 4.58-4.68 (comp, 5 H), 5.84-5.90 (m, 1 H), 6.64 (d, J = 8.5 Hz, 2 H), 6.66-6.72 (m, 1 H), 6.77 (d, J = 5.7 Hz, 2 H), 7.04 (d, J = 8.8 Hz, 2 H), 7.07 (s, 1 H), 7.20-7.34 (comp, 5 H), 7.91 (dd, J = 8.2, 13.6 Hz, 1 H). LR

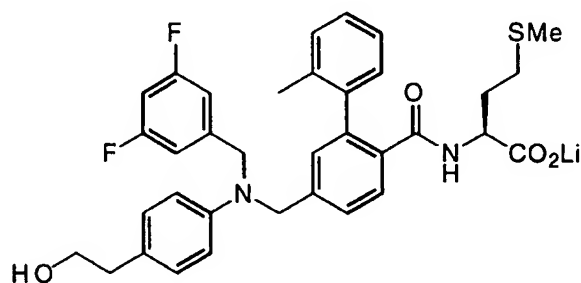
MS (ESI⁺): (M+H)⁺ calc for C₃₆H₃₉F₂N₂O₄S: 633; found: 633. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₆H₃₇F₂N₂O₄S: 631; found: 631. 1012A:

¹H NMR (CDCl₃): δ -0.04 (s, 6 H), 0.86 (s, 9 H), 1.52-1.64 (m, 1 H), 1.79-1.91 (m, 1 H), 1.99-2.12 (comp, 8 H), 2.71 (t, J = 7.2 Hz, 2 H), 3.65 (s, 3 H), 3.73 (t, J = 7.2 Hz, 2 H), 4.56 (s, 2 H), 4.60-4.70 (comp, 3 H), 5.83-5.89 (m, 1 H), 6.62 (d, J = 8.4 Hz, 2 H), 6.65-6.71 (m, 1 H), 6.76 (d, J = 6.1 Hz, 2 H), 7.01 (d, J = 8.4 Hz, 2 H), 7.06 (d, J = 1.7 Hz, 1 H), 7.20-7.34 (comp, 5 H), 7.90 (dd, J = 8.1, 13.2 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₄₂H₅₃F₂N₂O₄SiS: 747; found: 747. LR

MS (ESI⁻): (M-H)⁻ calc for C₄₂H₅₁F₂N₂O₄SiS: 745; found: 745.



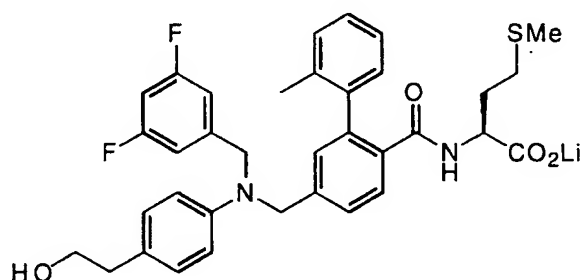
Example 1011B

N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-
2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1011B was prepared in the same fashion as 997D (76% yield).

¹H NMR (d₆-DMSO): δ 1.48-1.74 (br comp, 2 H), 1.90-2.06 (br comp, 8 H), 2.56 (t, J = 7.2 Hz, 2 H), 3.48 (t, J = 7.2 Hz, 2 H), 3.64-3.76 (br, 1 H), 4.69 (s, 2 H), 4.75 (s, 2 H), 6.58 (d, J = 8.5 Hz, 2 H), 6.90-7.22 (br comp, 10 H), 7.30 (d, J = 7.8 Hz, 1 H), 7.50 (d, J = 8.1 Hz, 1 H). HR

MS (FAB): (M+H)⁺ calc for C₃₅H₃₆F₂LiN₂O₄S: 625.2524; found: 625.2542 (2.8 ppm error).



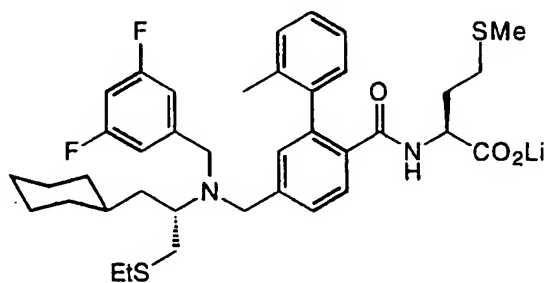
(258473) Example 1012B

N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-
2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1012B was prepared in the same fashion as 997D (64% yield).

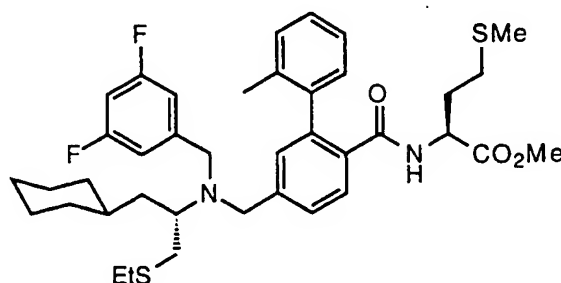
¹H NMR (d₆-DMSO): δ -0.12 (s, 6 H), 0.79 (s, 9 H), 1.48-1.74 (br comp, 2 H), 1.89-2.08 (br comp, 8 H), 2.56 (t, J = 6.9 Hz, 2 H), 3.65 (t, J = 6.9 Hz, 2 H), 4.69 (s, 2 H), 4.76 (s, 2 H), 6.58 (d, J = 8.9 Hz, 2 H), 6.88-7.22 (comp, 10 H), 7.30 (d, J = 7.7 Hz, 1 H), 7.49 (d, J = 7.7 Hz, 1 H). HR

MS (FAB): (M+H)⁺ calc for C₄₁H₅₀F₂LiN₂O₄SiS: 739.3389; found: 739.3389 (0.1 ppm error).



Example 1013

N-[4-N-3,5-difluorobenzyl-N-(1-ethylthio-3-cyclohexylprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl] methionine.



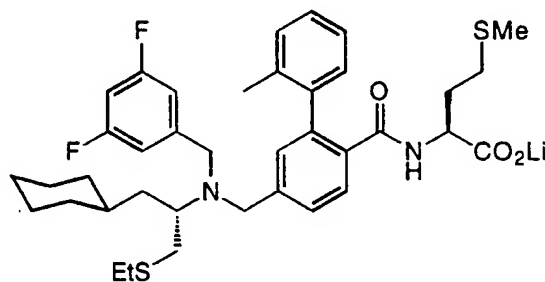
Example 1013A

Compound 1013A was prepared starting from 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) in the same fashion as 1004A (10% yield).

¹H NMR (CDCl₃): δ 0.70-0.93 (comp, 2 H), 1.06-1.71 (comp, 16 H), 1.30-1.92 (m, 1 H), 1.99-2.10 (comp, 7 H), 2.19 (s, 1 H), 2.39-2.48 (comp, 3 H), 2.77-2.89 (comp, 2 H), 3.58-3.71 (comp, 7 H), 4.56-4.70 (m, 1 H), 5.89 (d, J = 7.4 Hz, 1 H), 6.61-6.70 (m, 1 H), 6.94 (d, J = 8.1 Hz, 2 H), 7.15-7.22 (m, 1 H), 7.22-7.37 (comp, 9 H), 7.50 (d, J = 8.1 Hz, 1 H), 7.92 (dd, J = 8.1, 15.1 Hz, 1 H). LR

MS (ESI⁺): (M+H)⁺ calc for C₃₉H₅₁F₂N₂O₃S₂: 697; found: 697. LR

MS (ESI⁻): (M-H)⁻ calc for C₃₉H₄₉F₂N₂O₃S₂: 695; found: 695.



Example 1013B

N-[4-N-3,5-difluorobenzyl-N-(1-ethylthio-3-cyclohexylprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl] methionine.

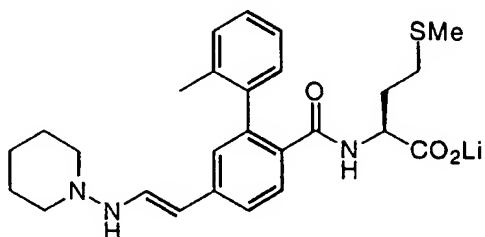
Compound 1013B was prepared in the same fashion as 997D (76% yield).

¹H NMR (d₆-DMSO): δ 0.59-0.74 (m, 1 H), 0.74-0.91 (m, 1 H), 0.97-1.18 (comp, 4 H), 1.21-1.33 (comp, 2 H), 1.36-1.75 (comp, 8 H), 1.76-1.87 (m, 1 H), 1.88-1.96 (comp, 2 H), 1.96-2.02 (comp, 2 H), 2.15-2.22 (br, 1 H), 2.34-2.45 (comp, 3 H), 2.60-2.70 (br, 1 H), 2.94 (dd, J = 5.9, 12.9 Hz, 1 H), 3.32-3.45 (comp, 4 H), 3.57-3.74 (br comp, 5 H),

6.93 (d, J = 6.3 Hz, 1 H), 7.03-7.25 (comp, 7 H), 7.38 (d, J = 7.3 Hz, 1 H), 7.50 (d, J = 7.7 Hz, 1 H). HR

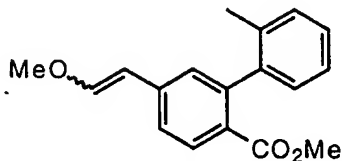
MS (FAB): (M+H)⁺ calc for C₃₈H₄₉F₂N₂O₃S₂: 683.3153; found: 683.3132 (-3.0 ppm error).

10115

Example 1014

N-[4-(2-N-piperidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10120

Example 1014A

A solution of (methoxymethyl)triphenylphosphonium chloride (15.6 g, 45.6 mmol) in tetrahydrofuran solvent (35 mL) was treated with sodium bis(trimethylsilyl)amide (45 mL of a 1 M tetrahydrofuran solution, 45 mmol), and the resulting deep red solution was treated with 4-formyl-2-(2-methylphenyl)benzoic acid, methyl ester, 1332A (7.30 g, 28.7 mmol). After 18 h the reaction mixture was diluted with diethyl ether solvent (100 mL) and filtered through silica gel with additional diethyl ether rinses. Flash column chromatography eluting with hexane and ethyl acetate using an elution gradient of 98:2 to 94:6 afforded 6.62 g of 1014A as a white solid (82% yield).

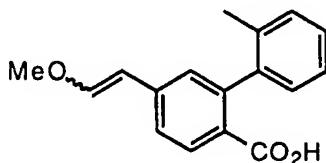
10125

10130

¹H NMR (CDCl₃): δ 2.06 (s, 3 H), 3.59 (s, 3 H), 3.70 (s, 3 H, E isomer), 3.79 (s, 3 H, Z isomer), 5.24 (d, J = 7.1 Hz, 1 H, Z isomer), 5.81 (d, J = 13.2 Hz, 1 H, E isomer), 6.23 (d, J = 7.1 Hz, 1 H, Z isomer), 7.06-7.10 (comp, 2 H), 7.16-7.64 (comp, 5 H), 7.90 (dd, J = 2.3, 8.4 Hz, 1 H). LR

10135

MS (ESI⁺): (M+H)⁺ calc for C₁₈H₁₉O₃: 283; found: 283.

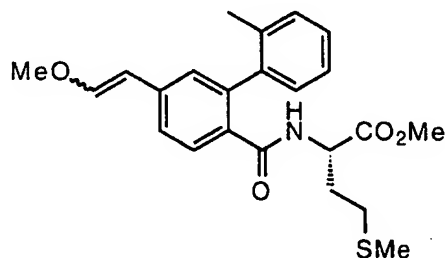


Example 1014B

A solution of 1014A (2.42 g, 8.57 mmol) in saturated methanolic LiOH (10 mL) was heated to reflux for 16 h. The reaction mixture was poured into H₂O (90 mL), and the resulting mixture was extracted with diethyl ether (3 x 30 mL). The aqueous layer was cooled to 0 °C with vigorous stirring and was slowly and carefully neutralized and then acidified to pH 4 by the addition of 3 M HCl. The cloudy solution was extracted with diethyl ether (3 x 30 mL), and the combined organic extracts were dried over MgSO₄ and then concentrated under reduced pressure to provide 1.81 g of 1014B as a white foam (79% yield). LR

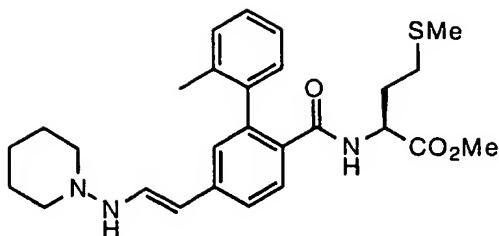
MS (ESI+): (M+H)⁺ calc for C₁₇H₁₇O₃: 269; found: 269. LR

MS (ESI-): (M-H)⁻ calc for C₁₇H₁₅O₃: 267; found: 267.

Example 1014C

A heterogeneous mixture of 1014B (1.81 g, 6.75 mmol), methionine methyl ester hydrochloride (2.72 g, 13.5 mmol), 1-hydroxybenzotriazole hydrate (HOBT) (4.56 g, 33.8 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (6.60 g, 33.8 mmol) in DMF solvent (40 mL) was treated with triethylamine (3.45 g, 33.8 mmol). The mixture was heated to 50 °C for 60 h, cooled to room temperature, diluted with ethyl acetate (200 mL), and extracted with 2:1:1 H₂O: saturated aqueous NaHCO₃: brine (200 mL + 2 x 100 mL), followed by brine (50 mL). The organic layer was dried over MgSO₄ and then concentrated under reduced pressure to yield an amber oil. Flash column chromatography eluting with hexane and ethyl acetate using an elution gradient of 80:20 to 70:30 afforded 2.55 g of 1014C as a colorless oil (91% yield).

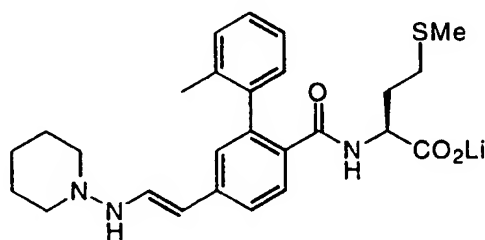
¹H NMR (CDCl₃): δ 1.51-1.63 (m, 1 H), 1.79-1.91 (m, 1 H), 1.99-2.21 (comp, 8 H), 3.65 (s, 3 H), 3.70 (s, 3 H, E isomer), 3.79 (s, 3 H, Z isomer), 4.56-4.67 (m, 1 H), 5.24 (d, J = 7.1 Hz, 1 H, E isomer), 5.82 (d, J = 12.9 Hz, 1 H, E isomer), 5.83-5.89 (m, 1 H), 7.00-7.36 (comp, 6 H), 7.12 (d, J = 12.9 Hz, 1 H, E isomer), 7.63-7.96 (comp, 1 H). LR MS (ESI+): (M+H)⁺ calc for C₂₃H₂₈O₄S: 414; found: 414.

Example 1014D

10170 A solution of 1014C (8.0 mL of a 0.1 M dioxane solution, 0.800 mmol) and H₂O (1.6 mL) was treated with p-toluenesulfonic acid hydrate (0.0309 g, 0.160 mmol). After 17 h the mixture was diluted with additional H₂O (12 mL) and then extracted with ethyl acetate (10 mL + 3 x 5 mL). The combined organic extracts were rinsed with brine (5 mL), dried over MgSO₄, and concentrated under reduced pressure to provide a pale yellow oil. The oil
 10175 was dissolved in benzene solvent (4 mL) and treated with Na₂SO₄ (0.454 g, 3.20 mmol), followed by 1-aminopiperidine (0.0991 g, 0.960 mmol), resulting in a bright yellow solution. After 18 h the reaction mixture was filtered through silica gel with ethyl acetate rinses and then concentrated under reduced pressure. Radial chromatography eluting with hexane and ethyl acetate using an elution gradient of 70:30 to 30:70 afforded 0.0342 g of
 10180 1014D as a colorless oil (8.9% yield).

¹H NMR (CDCl₃): δ 1.44-1.53 (comp, 2 H), 1.54-1.74 (comp, 5 H), 1.79-1.91 (m, 1 H), 1.99-2.10 (comp, 5 H), 2.18 (s, 1 H), 2.95 (app t, J = 5.6 Hz, 4 H), 3.62-3.67 (comp, 5 H), 4.56-4.67 (m, 1 H), 5.88 (d, J = 7.8 Hz, 1 H), 6.93-6.99 (m, 1 H), 7.06 (s, 1 H), 7.16-7.35 (comp, 6 H), 7.91 (dd, J = 8.2, 15.6 Hz, 1 H). LR

10185 MS (ESI⁺): (M+H)⁺ calc for C₂₇H₃₆N₂O₃S: 482; found: 482. LR
 MS (ESI⁻): (M-H)⁻ calc for C₂₇H₃₄N₃O₃S: 480; found: 480.

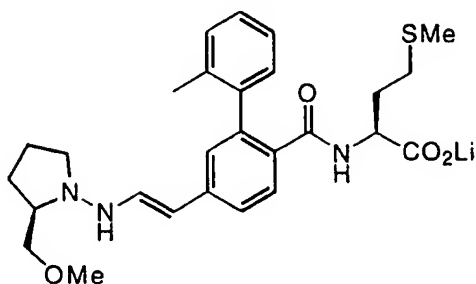
Example 1014E

10190 N-[4-(2-N-piperidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1014E was prepared in the same fashion as 997D (39% yield).

¹H NMR (d₆-DMSO): δ 1.36-1.45 (comp, 2 H), 1.50-1.76 (comp, 6 H), 1.76-2.20 (comp, 8 H), 2.84-2.90 (comp, 4 H), 3.53 (d, J = 5.8 Hz, 1 H), 3.62-3.72 (br, 1 H), 6.92 (d, J = 5.8 Hz, 1 H), 6.96-7.03 (comp, 2 H), 7.10-7.24 (comp, 4 H), 7.27 (dd, J = 1.4, 7.8 Hz, 1 H), 7.48 (d, J = 8.1 Hz, 1 H). HR

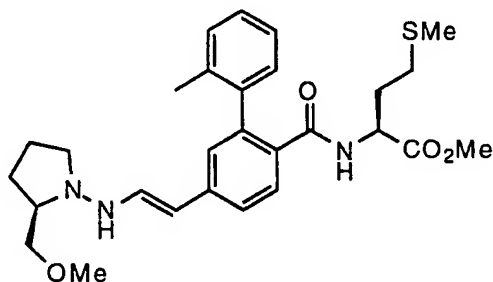
MS (FAB): (M+Li)⁺ calc for C₂₆H₃₃LiN₃O₃S: 474.2403; found: 474.2386 (-3.6 ppm error).



10200

Example 1015

N-[4-(2-N-2-methoxymethylpyrrolidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt



10205

Example 1015A

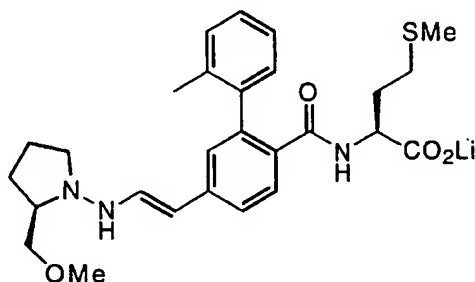
Compound 1015A was prepared in the same fashion as 1014D (11% yield).

¹H NMR (CDCl₃): δ 1.52-1.64 (m, 1 H), 1.71-2.20 (comp, 14 H), 2.72-2.84 (m, 1 H), 3.31-3.67 (comp, 12 H), 4.56-4.68 (m, 1 H), 5.88 (d, J = 7.3 Hz, 1 H), 6.64-6.70 (m, 1 H), 7.07 (s, 1 H), 7.17-7.35 (comp, 6 H), 7.91 (dd, J = 7.7, 15.4 Hz, 1 H). LR

10210

MS (ESI⁺): (M+H)⁺ calc for C₂₈H₃₈N₃O₄S: 512; found: 512. LR

MS (ESI⁻): (M-H)⁻ calc for C₂₈H₃₆N₃O₂S: 510; found: 510.



10215

Example 1015B

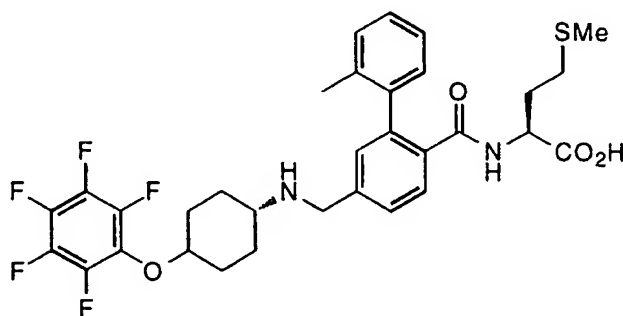
N-[4-(2-N-2-methoxymethylpyrrolidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1015B was prepared in the same fashion as 997D (50% yield).

¹H NMR (d₆-DMSO): δ 1.49-1.72 (comp, 3 H), 1.76-2.20 (comp, 10 H), 2.62-2.72 (m, 1 H), 3.19-3.55 (comp, 2 H), 3.62-3.74 (br, 1 H), 6.66 (app t, J = 5.5 Hz, 1 H), 6.89-6.94 (d, J = 5.5 Hz, 1 H), 7.02 (s, 1 H), 7.12-7.30 (comp, 5 H), 7.49 (d, J = 8.1 Hz, 1 H).

HR

MS (FAB): (M+Li)⁺ calc for C₂₇H₃₅LiN₃O₄S: 504.2508; found: 504.2509 (1.2 ppm error).



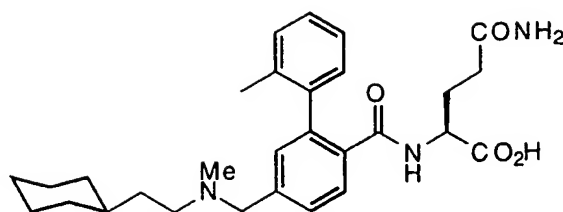
Example 1017

N-[4-N-(4-trans-pentafluorophenoxy)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

A solution of trans-4-aminocyclohexanol (3.03 g, 20.0 mmol) and diisopropylethylamine (7.4 mL, 42.0 mmol) in methylene chloride (30 mL) was treated with t-butyl dicarbonate (4.37 g, 20.0 mmol) over 5 minutes. The reaction stirred overnight at room temperature and was washed with 1 M HCl, 5% NaHCO₃, and brine to give the Boc-amine in nearly quantitative yield. A portion of this product (215 mg, 1.0 mmol) was combined with hexafluorobenzene (223 mg, 1.2 mmol) and 15-crown-5 (44 mg, 0.2 mmol) in DMF (3 mL) at room temperature. NaH (60% in oil, 4.4 mg, 1.2 mmol) was added and stirred overnight. Standard aqueous workup provided 149 mg of the protected pentafluorophenyl ether which was treated with excess TFA in methylene chloride, stripped to dryness, and reductively alkylated and saponified as described previously to provide 160 mg of the title compound.

MS m/e 635 (M-H)⁻.

¹H NMR (CDCl₃, 300 MHz) δ 1.5 (m, 4H), 1.79 (m, 1H), 2.05 (m, 12H), 2.81 (m, 1H), 4.05 (m, 4H), 6.25 (m, 1H), 6.81 (m, 2H), 7.1-7.7 (m, 7H).

**Example 1018**

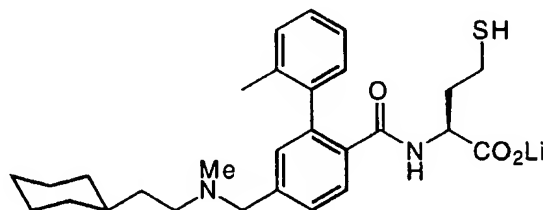
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]glutamine

Trifluoroacetic Acid salt

The compound was made by standard amino acid coupling of 4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid and L-Glu-OtBu followed by treatment with TFA.

MS m/e 492 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.91 (m, 2H), 1.1 (m, 4H), 1.63 (m, 9H), 1.9 (m, 3H), 2.1 (m, 3H), 2.71 (s, 3H), 3.1 (m, 2H), 4.09 (m, 1H), 4.29 (m, 1H), 4.43 (m, 1H); 6.74 (s, 1H), 7.1-7.22 (m, 3H), 7.39 (s, 1H), 7.60 (m, 2H), 8.32 (m, 2H), 9.62 (bs, 1H).

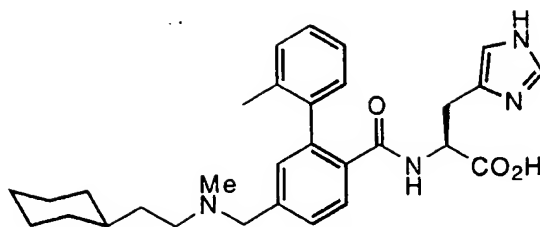
**Example 1019**

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]homocysteine, lithium salt

Prepared in a manner analogous to Example 1018 using L-homocysteine thiolactone and opening the resulting thiolactone with 1 equivalent of LiOH.

MS m/e 481 (M-H)⁻.

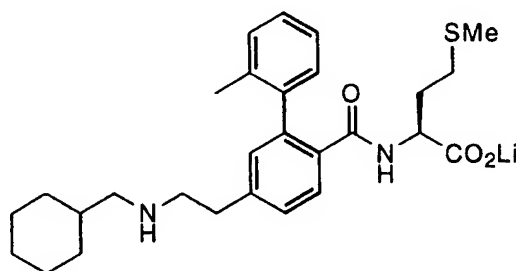
¹H NMR (d₆-DMSO, 300 MHz) δ 0.84 (m, 2H), 1.11 (m, 3H), 1.32 (m, 5H), 1.6 (m, 7H), 2.18 (m, 7H), 3.48 (s, 3H), 3.82 (m, 1H), 3.97 (m, 1H), 6.95 (m, 1H), 7.0-7.34 (m, 4H), 7.5 (m, 1H), 7.65 (m, 1H), 8.39 (m, 1H).

Example 1020N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]histidineTrifluoroacetic Acid salt

Prepared in a manner analogous to Example 1018 using L-His(trt)-OMe•HCl, removing the methyl ester with LiOH, and removing the im-trityl group with TFA/triethylsilane.

MS m/e 497 (M+H)⁺.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.90 (m, 2H), 1.17 (m, 4H), 1.63 (m, 8H), 1.99 (m, 6H), 2.1 (m, 3H), 2.73 (m, 3H), 3.0 (m, 2H), 4.3 (m, 1H), 4.4 (m, 1H), 4.56 (m, 2H), 7.08 (m, 1H), 7.15-7.42 (m, 3H), 7.58 (m, 2H), 8.62 (m, 1H), 8.97 (s, 1H).

Example 1021N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl] methionine methyl ester (84 mg, 0.17 mmol) was treated with LiOH (1 M, 85 μL) in methanol to provide the title compound.

MS m/e 481 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.83 (m, 2H), 1.15 (m, 4H), 1.36 (m, 1H), 1.62 (m, 9H), 1.98 (m, 10H), 3.7 (m, 2H), 4.27 (m, 1H), 6.90 (m, 1H), 7.00 (m, 1H), 7.1-7.3 (m, 4H), 7.44 (m, 1H), 8.24 (m, 1H).

N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl] methionine methyl ester

Methyl 4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoate hydrochloride (1.33 g, 3.31 mmol) was treated with sat. LiOH (1.3 mL, 6.95 mmol) in 50 mL methanol at 60 °C until no starting material remained by tlc. The solution was evaporated to dryness and treated with Met-OMe•HCl (0.99 g, 4.96 mmol), EDAC (1.26 g, 6.6 mmol), HOBt (1.5 g, 9.9 mmol), and TEA (to pH 6~7) in 25 mL DMF. Standard aqueous workup followed by flash chromatography (100 % EtOAc) provided 1.5 g of the title compound.

MS m/e 497 (M-H)⁻.

¹H NMR (CDCl₃, 300 MHz) δ 0.88 (m, 2H), 1.2 (m, 4H), 1.6 (m, 8H), 2.1 (m, 8H), 2.47 (m, 2H), 2.9 (m, 4H), 3.68 (s, 3H), 4.63 (m, 1H), 5.89 (d, 1H, J = 7 Hz), 7.04 (s, 1H), 7.19 (m, 1H), 7.3 (m, 4H), 7.91 (m, 1H).

Methyl 4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoate

Methyl 4-(propan-3-yl)-2-(2-methylphenyl)benzoate (5.0 g, 18.6 mmol) and cyclohexylmethylamine (2.32 g, 10.5 mmol) were dissolved in 250 mL 1 % acetic acid in methanol. After 10 minutes, sodium cyanoborohydride (1.76 g, 28 mmol) was added. The mixture stirred overnight at room temperature before evaporating to dryness. The residue was dissolved in ether and washed with 5 % NaHCO₃, water, and brine, dried over Na₂SO₄, and treated with anh. HCl. The oily product was crystalized from methanol and ether.

MS m/e 366 (M+H)⁺.

¹H NMR (CDCl₃, 300 MHz) δ 0.88 (m, 2H), 1.2 (m, 4H), 1.6 (m, 6H), 2.06 (s, 3H), 2.48 (d, 2H, J = 7 Hz), 2.92 (s, 4H), 3.61 (s, 3H), 7.06 (m, 1H), 7.23 (m, 5H), 7.92 (m, 1H).

Methyl 4-(propan-3-yl)-2-(2-methylphenyl)benzoate

Methyl 4-(prop-2-enyl)-2-(2-methylphenyl)benzoate (5.23 g, 19.6 mmol), osmium tetroxide (0.02 mmol/mL t-BuOH, 29.5 mL), and sodium periodate (10.5 g, 49.1 mmol) were combined in 200 mL acetone with 50 mL water. After stirring at ambient temperature for 1 hour, the mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na₂SO₄ to give the desired product which was used directly in the next step.

MS m/e 286 (M+NH₄)⁺.

¹H NMR (CDCl₃, 300 MHz) δ 2.06 (m, 3H), 3.61 (s, 3H), 3.8 (m, 2H), 7.1 (m, 1H), 7.25 (m, 5H), 7.95 (m, 1H), 9.80 (m, 1H).

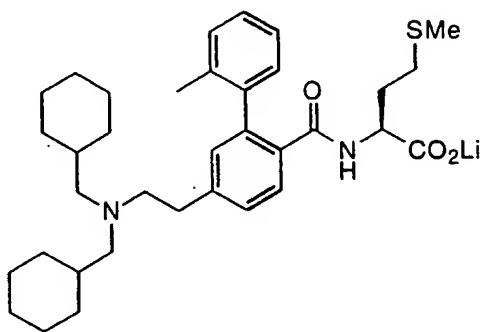
Methyl 4-(prop-2-enyl)-2-(2-methylphenyl)benzoate

10335 Methyl 4-iodo-2-(2-methylphenyl)benzoate (10.0 g, 28.4 mmol), allyltributyl tin (11.3 g, 34.1 mmol), and dichlorobis(triphenylphosphine)palladium (II) (1.0 g, 1.42 mmol) were combined in 50 mL toluene and 20 mL NMP and heated at 125 °C for 18 hours. The reaction was diluted with EtOAc, washed with water and brine, dried over Na₂SO₄, and chromatographed (5 % EtOAc in hexanes) to provide the title compound in 74
10340 % yield.

MS m/e 284 (M+NH₄)⁺.

¹H NMR (CDCl₃, 300 MHz) δ 2.06 (s, 3H), 3.45 (d, 2H, J = 7 Hz), 3.61 (s, 3H), 5.1 (m, 2H), 5.97 (m, 1H), 7.08 (m, 1H), 7.23 (m, 5H), 7.94 (m, 1H).

10345



Example 1022

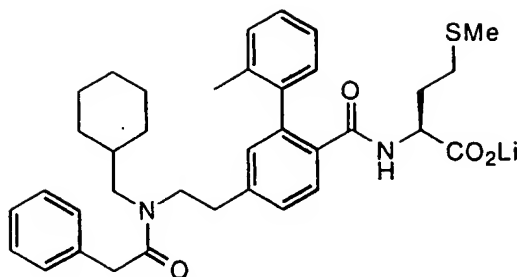
N-[4-(N,N-di-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt

10350 N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl] methionine methyl ester (300 mg, 0.60 mmol) and cyclohexylcarboxaldehyde (140 mg, 1.21 mmol) were dissolved in 1 % acetic acid in methanol (5 mL) and treated with sodium cyanoborohydride (76 mg, 1.21 mmol). Standard workup followed by flash chromatography (20 % ethyl acetate in hexane) provided 320 mg which was subsequently
10355 saponified with LiOH to the title compound.

MS m/e 577 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.75 (m, 4H), 1.10 (m, 8H), 1.30 (m, 2H), 1.61 (m, 9H), 2.0 (m, 10H), 2.6 (m, 2H), 2.7 (m, 2H), 3.3 (m, 1H), 3.68 (m, 1H), 6.90 (m, 2H), 7.1 (m, 5H), 7.44 (m, 1H).

10360



Example 1023

N-[4-(N-(cyclohexylmethyl)-N-phenylacetamidoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10365

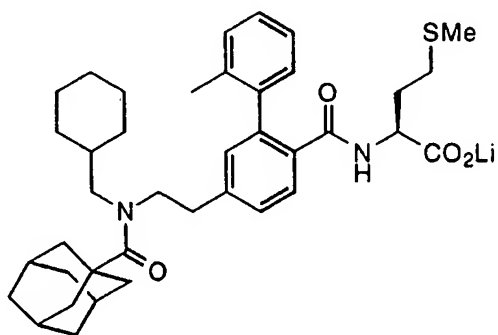
N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl] methionine methyl ester (75 mg, 0.11 mmol), phenacetyl chloride (26 mg, 0.17 mmol), and triethylamine (17 mg, 0.15 mmol) were stirred in DMF (0.5 mL) for 18 hours at ambient temperature. The reaction was diluted with EtOAc, washed with 5 % NaHCO₃, water, and brine, dried over Na₂SO₄, and chromatographed (50 % EtOAc/hexanes) to provide 66 mg of the methyl ester of the title compound. This was subsequently saponified with LiOH in quantitative yield to the title compound.

10370

MS m/e 599 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.83 (m, 2H), 1.15 (m, 4H), 1.6 (m, 9H), 1.98 (m, 8H), 2.8 (m, 1H), 3.1 (m, 2H), 3.5 (m, 3H), 3.7 (m, 2H), 7.0 (m, 2H), 7.1-7.3 (m, 9H), 7.45 (m, 1H).

10375



Example 1024

N-[4-(N-(cyclohexylmethyl)-N-1-adamantanoylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10380

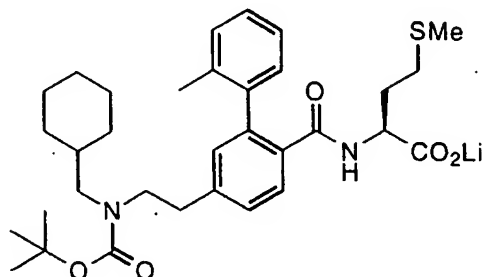
This compound was prepared in a manner analogous to Example 1023 using 1-adamantanecarbonyl chloride.

10385

MS m/e 643 (M-H)⁻.

^1H NMR (d_6 -DMSO, 300 MHz) δ 0.87 (m, 8H), 1.15 (m, 4H), 1.6 (m, 14H), 1.9 (m, 12H), 2.85 (m, 1H), 3.18 (m, 2H), 3.6 (m, 2H), 6.91 (m, 1H), 7.02 (m, 1H), 7.2 (m, 5H), 7.48 (m, 1H).

10390

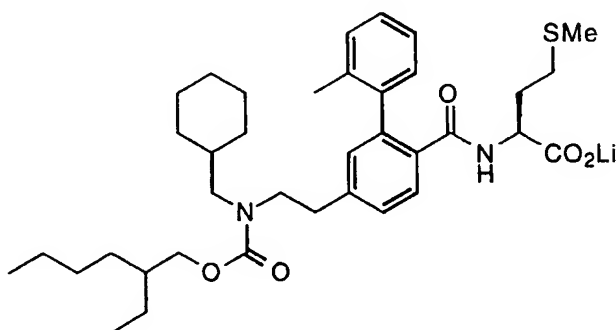
Example 1025

N-[4-(N-cyclohexylmethyl-N-t-butoxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10395 This compound was prepared in a manner analogous to Example 1023 using di-
butyldicarbonate.

MS m/e 581 (M-H) $^-$.

^1H NMR (d_6 -DMSO, 300 MHz) δ 0.83 (m, 2H), 1.15 (m, 4H), 1.38 (s, 9H), 1.6 (m, 9H), 1.95 (m, 6H), 2.18 (m, 2H), 2.8 (m, 4H), 3.7 (m, 1H), 6.9 (m, 1H), 7.0 (m, 1H),
10400 7.2 (m, 5H), 7.45 (m, 1H).

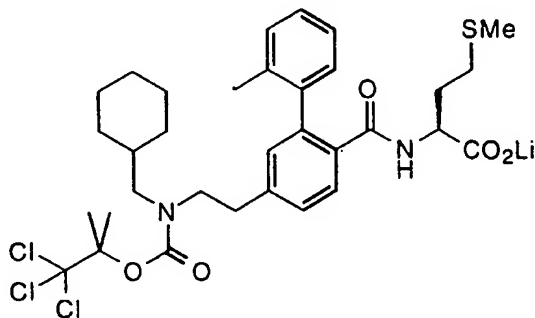
Example 1026

10405 N-[4-(N-cyclohexylmethyl-N-2-ethylhexyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023 using 2-ethylhexyl chloroformate.

MS m/e 637 (M-H) $^-$.

10410 ^1H NMR (d_6 -DMSO, 300 MHz) δ 0.83 (m, 4H), 1.15 (m, 4H), 1.23 (m, 9H), 1.6 (m, 9H), 1.95 (m, 8H), 2.83 (m, 2H), 3.0 (m, 2H), 3.5 (m, 3H), 3.6 (m, 1H), 3.89 (m, 2H), 4.29 (m, 1H), 6.9 (m, 1H), 7.0 (m, 1H), 7.2 (m, 5H), 7.45 (m, 1H).



10415

Example 1027

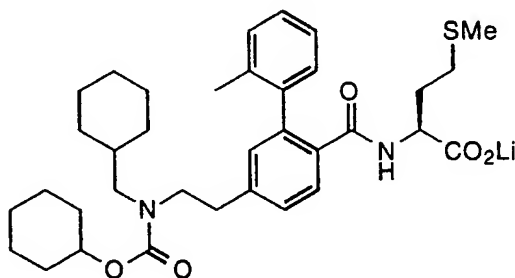
N-[4-(N-cyclohexylmethyl-N-2,2,2-trichloroethoxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023.

10420 MS m/e 683 (M-H) $^-$.

^1H NMR (d_6 -DMSO, 300 MHz) δ 0.84 (m, 2H), 1.17 (m, 4H), 1.6 (m, 5H), 1.9 (m, 14H), 2.9 (m, 3H), 3.03 (m, 1H), 3.5 (m, 3H), 3.6 (m, 1H), 4.28 (m, 1H), 6.9 (m, 1H), 7.0 (m, 2H), 7.2 (m, 5H), 7.45 (m, 1H).

10425



Example 1028

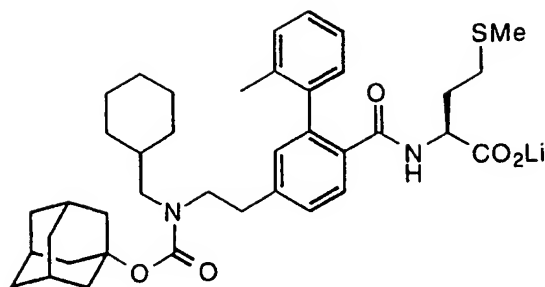
N-[4-(N-cyclohexylmethyl-N-cyclohexyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10430 This compound was prepared in a manner analogous to Example 1023.

MS m/e 607 (M-H) $^-$.

^1H NMR (d_6 -DMSO, 300 MHz) δ 0.84 (m, 4H), 1.17 (m, 4H), 1.3 (m, 6H), 1.6 (m, 10H), 1.95 (m, 8H), 2.17 (m, 1H), 2.9 (m, 4H), 3.6 (m, 1H), 4.53 (m, 1H), 6.9 (m, 1H), 7.0 (m, 1H), 7.2 (m, 5H), 7.47 (m, 1H).

10435

Example 1029

N-[4-(N-cyclohexylmethyl-N-adamantylloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

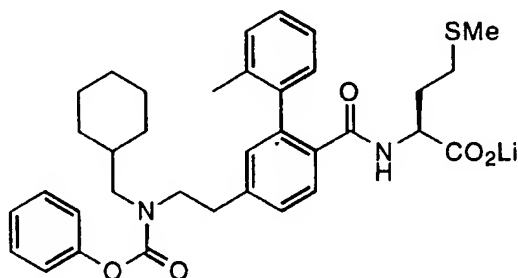
10440

This compound was prepared in a manner analogous to Example 1023.

MS m/e 659 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.83 (m, 6H), 1.16 (m, 6H), 1.6 (m, 13H), 2.0 (m, 12H), 2.82 (m, 3H), 2.95 (m, 1H), 3.65 (m, 2H), 6.95 (m, 2H), 7.2 (m, 5H), 7.47 (m, 1H).

10445

Example 1030

10450

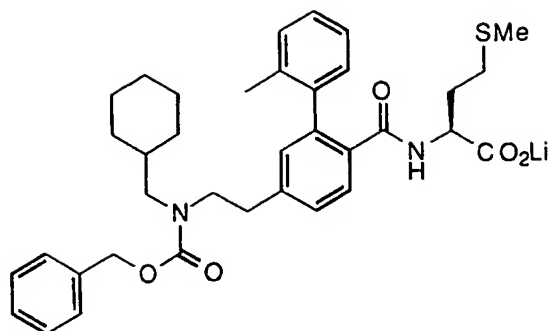
N-[4-(N-cyclohexylmethyl-N-phenoxy carbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023.

MS m/e 601 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.91 (m, 2H), 1.19 (m, 4H), 1.63 (m, 9H), 1.98 (m, 6H), 2.15 (m, 2H), 2.97 (m, 1H), 3.11 (m, 1H), 3.5 (m, 1H), 3.7 (m, 2H), 6.85-7.39 (m, 12H), 7.48 (m, 1H).

10455



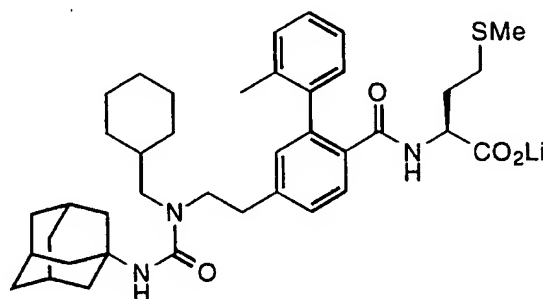
Example 1031

N-[4-(N-cyclohexylmethyl-N-benzyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023.

MS m/e 615 (M-H)⁺.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.83 (m, 2H), 1.13 (m, 4H), 1.6 (m, 6H), 1.95 (m, 6H), 2.14 (m, 2H), 2.83 (m, 2H), 2.99 (m, 2H), 3.40 (m, 2H), 3.65 (m, 2H), 5.04 (m, 2H), 6.9-7.3 (m, 12H), 7.43 (m, 1H).



Example 1032

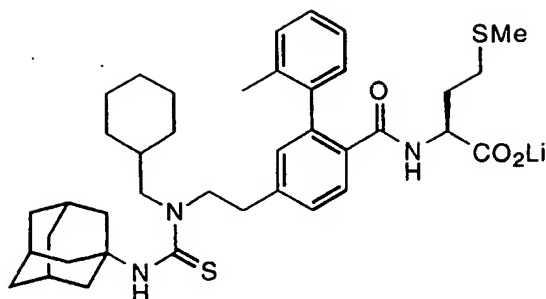
N-[4-(N-cyclohexylmethyl-N-adamant-1-aminocarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023 using

adamantyl isocyanate.

MS m/e 658 (M-H)⁺.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.83 (m, 6H), 1.13 (m, 6H), 1.6 (m, 13H), 1.95 (m, 12H), 2.18 (m, 1H), 2.79 (m, 2H), 2.91 (m, 2H), 3.65 (m, 2H), 6.9 (m, 1H), 7.0 (m, 1H), 7.2 (m, 5H), 7.46 (m, 1H).

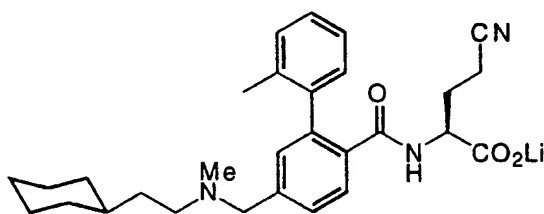
**Example 1033**

N-[4-(N-cyclohexylmethyl-N-adamant-1-aminothiocarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023 using adamantyl isothiocyanate.

MS m/e 674 (M-H)⁻.

¹H NMR (d₆-DMSO, 300 MHz) δ 0.85 (m, 6H), 1.15 (m, 6H), 1.6 (m, 13H), 2.0 (m, 12H), 2.2 (m, 1H), 2.74 (m, 2H), 2.91 (m, 2H), 3.62 (m, 2H), 6.9-7.5 (m, 8H).

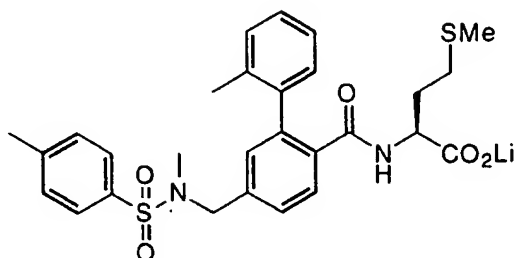
**Example 1041**

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]glutaminitrile, lithium salt

Boc-Gln (2.0 g, 8.11 mmol) and acetic anhydride (0.92 mL, 9.7 mmol) were combined in dry pyridine (10 mL) and stirred at room temperature overnight. The solution was evaporated to dryness and partitioned between EtOAc and 10 % citric acid. The organic layer was washed with 10 % citric acid, water, and brine, dried over Na₂SO₄, and evaporated to dryness. The residue was dissolved in MeOH (5 mL) and treated with trimethylsilyldiazomethane (2.0 M in hexanes, excess). The mixture was evaporated and chromatographed (50 % EtOAc in hexanes) to give 0.92 g of Boc-glutaminitrile methyl ester. The nitrile (0.24 g, 1 mmol) was treated with excess 50 % trifluoroacetic acid in methylene chloride, evaporated and coupled to 4-(2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid via standard techniques, followed by standard lithium hydroxide saponification to provide the title compound.

MS m/e 474 (M-H)⁻.

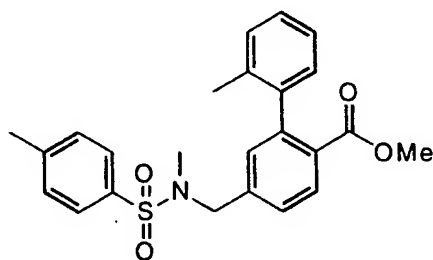
¹H NMR (d₆-DMSO, 300 MHz) δ 0.82 (m, 2H), 1.11 (m, 3H), 1.32 (m, 5H), 1.6 (m, 7H), 2.18 (m, 6H), 2.32 (m, 1H), 2.58 (m, 1H), 2.75 (m, 1H), 3.53 (m, 2H), 6.9-7.5 (m, 7H), 7.83 (m, 1H).



10515

Example 1047

N-[4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt



10520

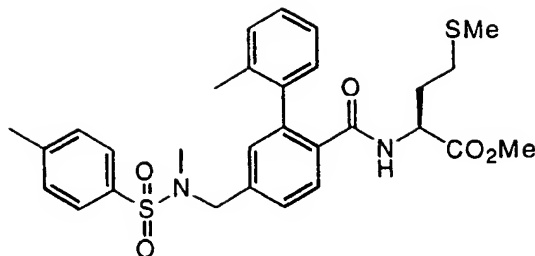
Example 1047A

4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

To a solution of N-methyl-p-toluenesulfonamide (203mg) and 4-hydroxymethyl-2-(2-methylphenyl)benzoic acid methyl ester (example 1178C, 255mg) in THF (3mL) at 0°C was added triphenylphosphine (315mg) and diethyl azodicarboxylate (0.19mL). The reaction was warmed, and stirred at ambient temperature for 30h. The reaction was concentrated, and the residue was purified by silica gel chromatography eluting with a gradient from 20% EtOAc/hexane to 100% EtOAc. The product was isolated as a colorless oil (170mg, 40%).

10530

MS (DCI/NH₃) 441 (M+NH₄)⁺.

Example 1047B

N-[4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

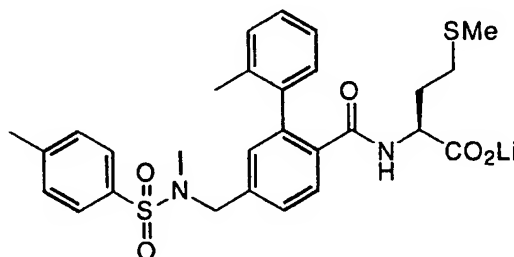
10535

4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted to the title compound according to the procedures in examples 608C and D.

MS (APCI(+)) m/e (M+H)⁺ 555,

10540

MS (APCI(-)) m/e (M-H)⁻ 553.

Example 1047C

N-[4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10545

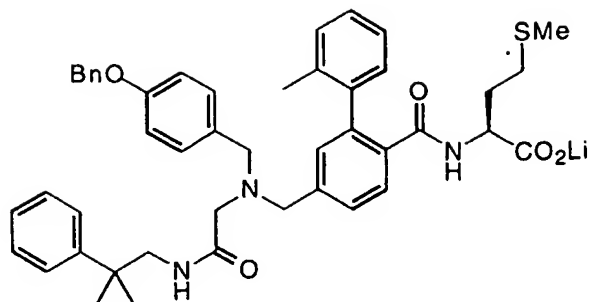
N-[4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound by the procedure in example 608E. The product was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 1.50-1.88 (m, 4H), 1.92 (s, 3H), 1.95-2.14 (m, 3H), 2.41 (s, 3H), 2.59 (s, 3H), 3.58-3.70 (m, 1H), 4.18 (s, 2H), 6.96 (brd, J=5.4 Hz, 1H), 7.02-7.26 (m, 5H), 7.35 (d, J=8.1 Hz, 1H), 7.44 (d, J=7.8 Hz, 2H), 7.52 (d, J=8.1 Hz, 1H), 7.72 (d, J=7.8 Hz, 2H).

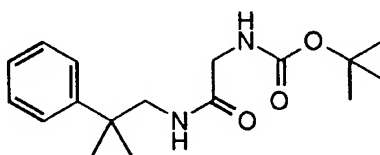
10550

MS (ESI(-)) m/e 539 (M-H); Analysis calc'd for C₂₈H₃₁LiN₂O₅S₂•1.50H₂O: C, 58.63; H, 5.97; N, 4.88; found: C, 58.61; H, 5.66; N, 4.51.

10555

Example 1048

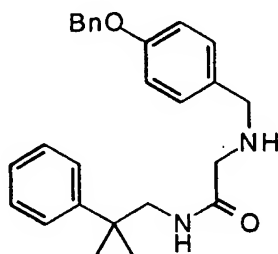
N-[4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Example 1048A

N-(2-Methyl-2-phenylpropyl)-N-tert-butoxycarbonyl-2-aminoacetamide

10565 To a slurry of NaH (10g of a 60% dispersion in mineral oil) in dry THF (300mL) was added benzyliodide (10g) by means of a dropping funnel. Cautious addition of methyl iodide (13mL) caused rapid gas evolution and an increase in temperature which was moderated with an ice bath. After stirring at ambient temperature for 12h, the reaction was quenched cautiously with water (100mL). The mixture was diluted with ether (500mL) and the layers were separated. The ether layer was washed with water (100mL) containing a small amount of Na₂SO₃ to eliminate the iodine color, then washed with brine (50mL). The organic solution was dried (MgSO₄), filtered and concentrated to afford an oil. This material was added neat to a solution of 1M LiAlH₄ (85mL, THF) in ether (100mL). If necessary, the reduction was initiated after a small amount of starting material was added by warming with a heat gun. The starting material was then added at a rate which maintained a gentle reflux. After addition was complete, the reaction was stirred without heating or cooling for 1h. The reaction was cautiously quenched with vigorous stirring by the addition of water (3.2mL), 15%NaOH (3.2mL), and more water (10mL). The suspension was filtered through celite, which was rinsed with ether. The filtrate was concentrated to give an oil (ca. 20g) which contained mineral oil from the sodium hydride dispersion. A portion of this material (3.3g) was dissolved in DMF (67mL) along with N-(tert-butoxycarbonyl)glycine (3.5g), followed by addition of N-methylmorpholine (3.3mL), 1-hydroxybenzotriazole (3.0g), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (5.0g). After stirring at ambient temperature for 15h, the reaction was poured into ether (500mL), washed with water

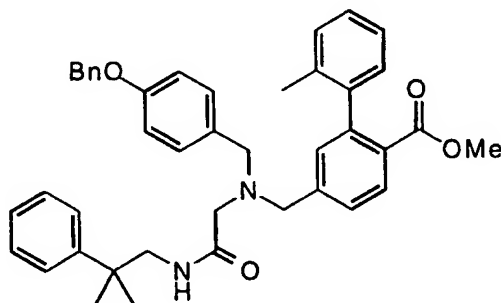
10585 (2X100mL), 1M HCl (2X100mL), saturated NaHCO₃ (2X50mL), and brine (100mL). The organic solution was dried (MgSO₄), filtered and concentrated to afford a residue which partly solidified. The residue was triturated with hexane, and filtered to give 4.5g of the title compound. MS(DCI/NH₃) 307 (M+H)⁺.



10590

Example 1048BN-(2-Methyl-2-phenylpropyl)-N-(4-benzyloxybenzyl)-2-aminoacetamide

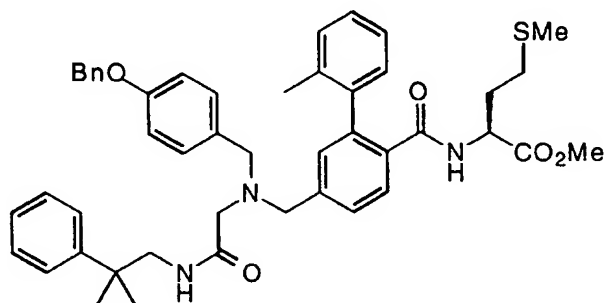
To a solution of N-(2-methyl-2-phenylpropyl)-N-tert-butoxycarbonyl-2-aminoacetamide (4.5g) in dichloromethane (50mL) was added trifluoroacetic acid (10mL).
 10595 After 1.5h at ambient temperature, the reaction was concentrated, then the residue was evaporated from toluene to afford a light tan solid (4.4g). This material was stirred with 4-benzyloxybenzaldehyde (3.27g) in 1:1 THF:EtOH (30mL). Bromocresol green (1mg) was added, and the reaction was adjusted to pH≈3 with 15%NaOH. The reaction was warmed briefly to reflux to complete dissolution of starting material, then cooled to ambient
 10600 temperature. Sodium cyanoborohydride (15mL, 1M THF) was added, and the reaction color was held at a light green by addition of a 2:1 ethanol:HCl mixture. After starting aldehyde was consumed (TLC), the reaction was concentrated, dissolved in EtOAc (200mL), and washed with saturated NaHCO₃ (2X50mL), water (50mL), and brine (50mL). The organic solution was dried (MgSO₄), filtered and concentrated, and the residue
 10605 was purified by silica gel chromatography to give the title compound (1.96g) along with a significant amount of double alkylation product. MS(ESI) 403 (M+H)⁺.

Example 1048C

10610 4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)aminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

The title compound was prepared by the procedure in example 608B, replacing N-methylcyclohexylethylamine with N-(2-methyl-2-phenylpropyl)-N-(4-benzyloxybenzyl)-2-aminoacetamide. MS(APCI(+)) 641 (M+H)⁺. MS(APCI(-)) 675 (M+Cl)⁻.

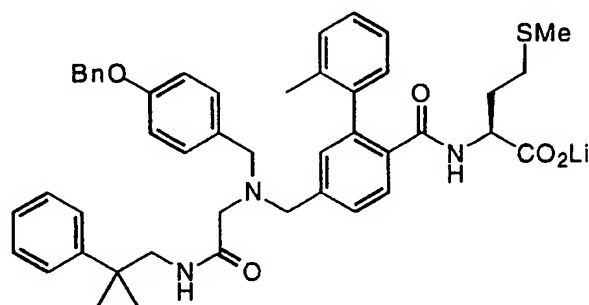
10615



Example 1048D

N-[4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

10620 4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylamino)acetylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted to the title compound according to the procedures in examples 608C and D. MS(APCI(+)) 772 (M+H)⁺. MS(APCI(-)) 806 (M+Cl)⁻.



10625

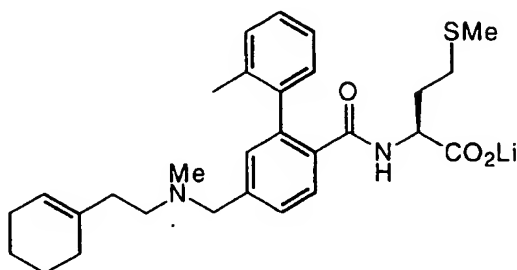
Example 1048E

N-[4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10630 N-[4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylamino)acetylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound by the procedure in example 608E. The product was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 1.15 (s, 3H), 1.16 (s, 3H), 1.50-1.84 (m, 5H), 1.92 (s, 3H), 1.95-2.16 (m, 3H), 2.88 (s, 2H), 3.28 (s, 2H), 3.39 (s, 2H), 3.47 (s, 2H), 3.60-

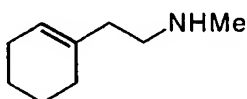
10635 3.68 (m, 1H), 5.07 (s, 2H), 6.87 (d, J=9 Hz, 2H), 6.93 (d, J=9 Hz, 2H), 6.93-7.48 (m, 17H). Analysis calc'd for $C_{46}H_{50}LiN_3O_5S \cdot 1.95H_2O$: C, 69.15; H, 6.80; N, 5.26; found: C, 69.11; H, 6.50; N, 5.13.



10640

Example 1056

N-[4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt



10645

Example 1056A

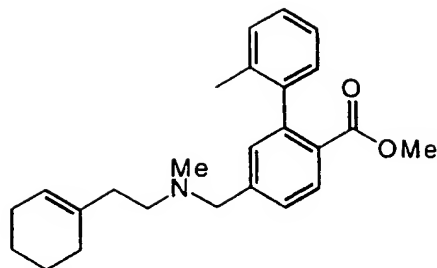
N-Methyl-2-(1-cyclohexenyl)ethylamine

To a solution of 2-(1-cyclohexenyl)ethylamine (4.0g) in 1,4-dioxane (40mL) was added di-tert-butyl dicarbonate (7.7g). After gas evolution ceased (≈ 2 h) the reaction was concentrated. A portion of the residue (2g) was dissolved in THF (10mL) followed by addition of $LiAlH_4$ (10mL, 1M THF), which caused an exotherm. After 3h, more $LiAlH_4$ solution was added (4mL), and the reaction was warmed to reflux. After 1h, the reaction was cooled, and quenched cautiously with vigorous stirring by the addition of water (0.57mL), 1M NaOH (0.6mL), and more water (1.5mL). The suspension was filtered through celite, which was washed with ether. The organic solution was concentrated to give the desired product as a volatile oil (0.8g).

10650

10655

1H NMR (300 MHz, $CDCl_3$) δ 1.52-1.67 (m, 4H), 1.89-2.04 (m, 4H), 2.14 (brt, J=7 Hz, 2H), 2.42 (s, 3H), 2.63 (t, J=7 Hz, 2H), 5.45 (m, 1H).

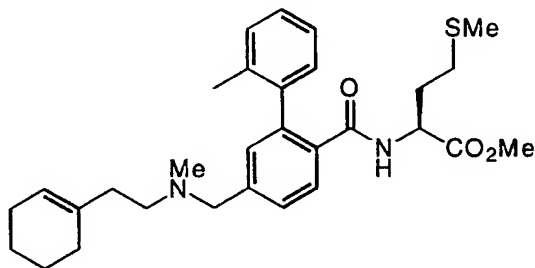


10660

Example 1056B4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid,Methyl Ester

The title compound was prepared from N-methyl-2-(1-cyclohexenyl)ethylamine
 according to the procedure in example 608B.

MS (DCI/NH₃) 378 (M+H)⁺.

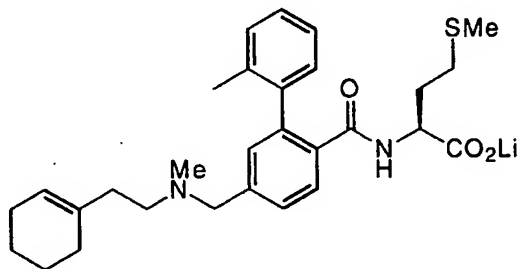
Example 1056C

10670

N-[4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, Methyl Ester

The title compound was prepared from 4-(N-(2-cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester according to the procedure in examples 608C and D. MS(APCI(+)) 509 (M+H)⁺. MS(APCI(-)) 543

(M+Cl)⁻.

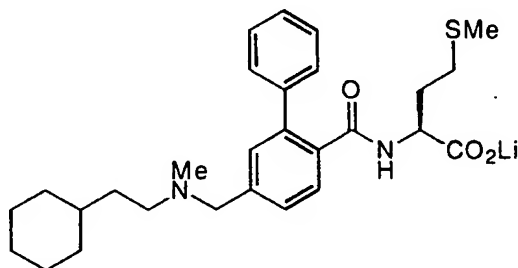
Example 1056D

10680

N-[4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

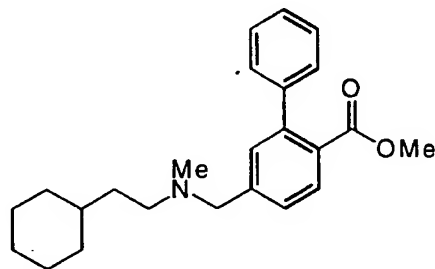
N-[4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted into the title compound by the procedure in example 608E, and was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 1.38-1.75 (m, 4H), 1.80-2.13 (m, 13H), 1.91 (s, 3H), 2.14 (s, 3H), 2.36-2.45 (m, 2H), 3.50 (s, 2H), 3.56-3.67 (brs, 1H), 5.32-5.36 (m, 1H), 6.88-6.92 (m, 1H), 7.05-7.23 (m, 5H), 7.32 (d, J=8.1 Hz, 1H), 7.48 (d, J=8.1 Hz, 1H). MS (APCI(-)) m/e 493 (M-H); Analysis calc'd for C₂₉H₃₇LiN₂O₃S•1.15H₂O: C, 66.81; H, 7.60; N, 5.37; found: C, 66.86; H, 7.34; N, 5.19.



Example 1057

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]methionine, lithium salt

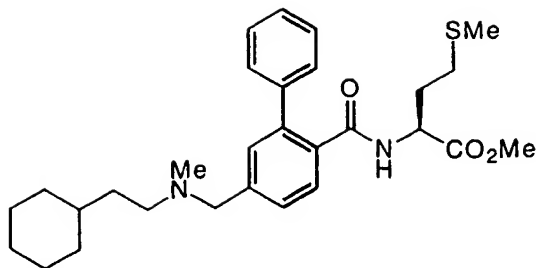


Example 1057A

4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoic acid, Methyl Ester

The title compound was prepared according to the procedure in example 608B, replacing 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester with 4-bromomethyl-2-phenylbenzoic acid methyl ester (example 228B).

MS (DCI/NH₃) 366 (M+H)⁺.

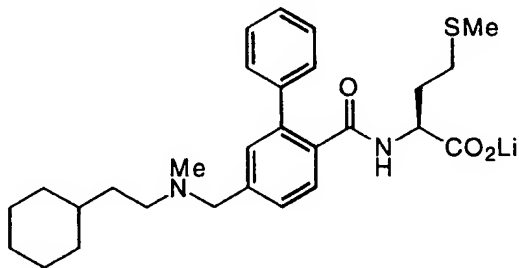


10705

Example 1057BN-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]methionine, Methyl Ester

10710

The title compound was prepared from 4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoic acid methyl ester according to the procedure in examples 608C and D. MS(APCI(+)) 497 (M+H)⁺. MS(APCI(-)) 531 (M+Cl)⁻.

Example 1057CN-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]methionine, lithium salt

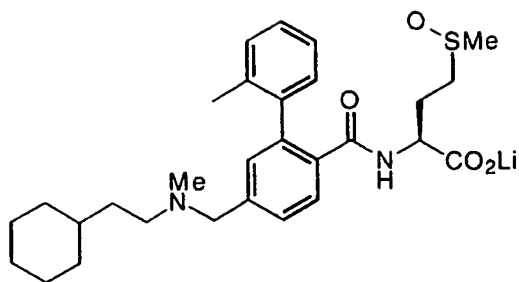
10715

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]methionine methyl ester was converted into the title compound according to the procedure in example 608E, and was isolated as a white powder.

10720

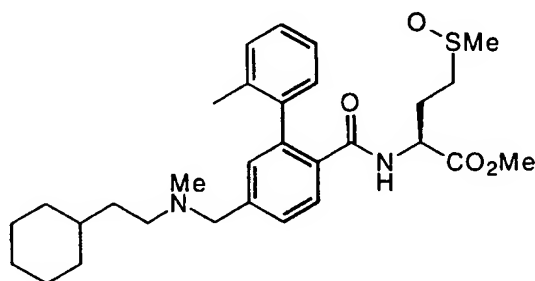
¹H NMR (300 MHz, DMSO) δ 0.76-0.92 (m, 2H), 1.06-1.38 (m, 5H), 1.53-1.67 (m, 6H), 1.67-1.89 (m, 2H), 1.97 (s, 3H), 1.98-2.20 (m, 2H), 2.14 (s, 3H), 2.36 (t, J=6 Hz, 2H), 3.51 (s, 2H), 3.76-3.82 (m, 1H), 7.16 (d, J=6 Hz, 1H), 7.27-7.41 (m, 8H). MS (APCI(-)) m/e 481 (M-H); Analysis calc'd for C₂₈H₃₇LiN₂O₃S•0.95H₂O: C, 66.50; H, 7.75; N, 5.54; found: C, 66.53; H, 7.58; N, 5.47.

10725

Example 1058

(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt

10730

Example 1058A

(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoic acid, Methyl Ester

10735

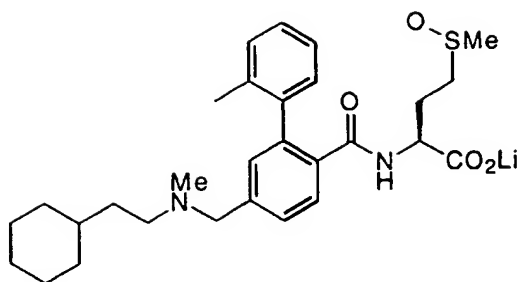
To a solution of N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester (example 608D, 100mg) in dichloromethane (2mL) at ambient temperature was added trifluoroacetic acid (0.023ml), and the salt solution was cooled to 0°C. Hydrogen peroxide (30%, 0.050mL) was added with vigorous stirring. After 42h at ambient temperature, the reaction was concentrated and the residue was purified

10740

by silica gel chromatography eluting with 2.5%-5.0%-10.0% MeOH/CH₂Cl₂, to give two products which were both colorless oils. The more mobile product is (2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoic acid methyl ester (35mg, 33%). MS(APCI(+)) 543 (M+H)⁺. MS(APCI(-)) 577 (M+Cl)⁻. The less mobile product is the title compound (50mg, 48%).

10745

MS(APCI(+)) 527 (M+H)⁺. MS(APCI(-)) 561 (M+Cl)⁻.

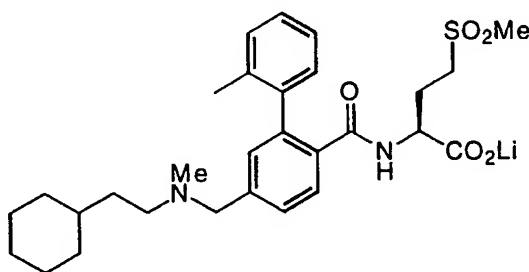
Example 1058B

(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt

(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoic acid methyl ester was converted to the title compound according to the procedure in example 608E, with the exception that the product was isolated as a white powder after trituration of the concentrated reaction residue with diethyl ether and drying under vacuum.

¹H NMR (300 MHz, DMSO) δ 0.76-0.90 (m, 2H), 1.04-1.37 (m, 5H), 1.53-1.65 (m, 6H), 1.66-1.90 (m, 2H), 1.95-2.22 (m, 5H), 2.13 (s, 3H), 2.32 (t, J=7.2 Hz, 2H), 2.37 (s, 1.5H), 2.39 (s, 1.5H), 3.49 (s, 2H), 3.64-3.77 (m, 1H), 6.99 (d, J=6 Hz, 1H), 7.06-7.26 (m, 5H), 7.32 (d, J=7.5 Hz, 1H), 7.50 (d, J=8.1 Hz, 0.5H), 7.51 (d, J=8.1 Hz, 0.5H).

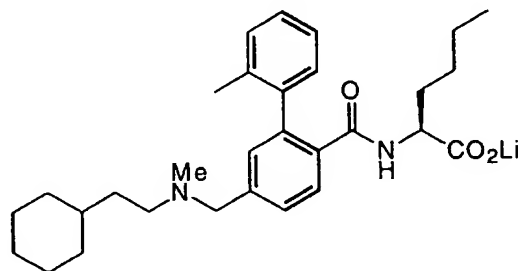
MS (ESI(-)) m/e 511 (M-H).

Example 1059

(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt

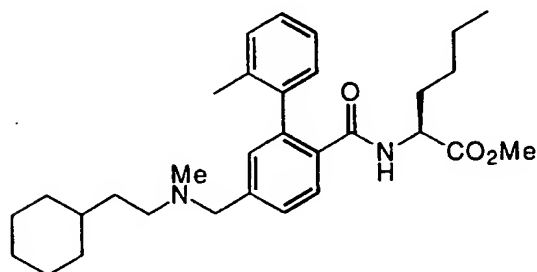
(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoic acid methyl ester (example 1058A) was converted to the title compound according to the procedure in example 608E, with the exception that the product was isolated as a white powder after trituration of the concentrated reaction residue with diethyl ether and drying under vacuum.

¹H NMR (300 MHz, DMSO) δ 0.76-0.91 (m, 2H), 1.08-1.37 (m, 5H), 1.53-1.67 (m, 6H), 1.72-1.93 (m, 2H), 1.95-2.20 (m, 3H), 2.16 (s, 3H), 2.36 (t, J=7.2 Hz, 2H), 2.42-2.56 (m, 2H), 2.83 (s, 3H), 3.52 (s, 2H), 3.64-3.77 (m, 1H), 6.98 (d, J=6 Hz, 1H), 7.04-7.28 (m, 5H), 7.34 (d, J=8.1 Hz, 1H), 7.54 (d, J=8.1 Hz, 1H).
 MS (ESI(-)) m/e 527 (M-H); Analysis calc'd for C₂₉H₃₉LiN₂O₅S•0.15H₂O•0.40HoAc: C, 60.32; H, 6.82; N, 4.74; found: C, 60.25; H, 6.97; N, 4.92.



Example 1060

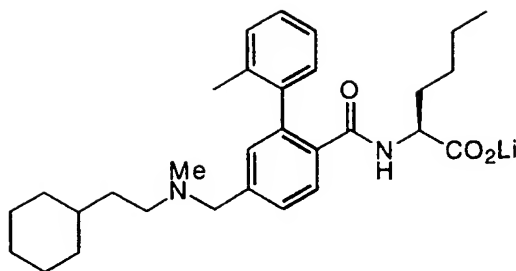
N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]norleucine, lithium salt



Example 1060A

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]norleucine, Methyl Ester

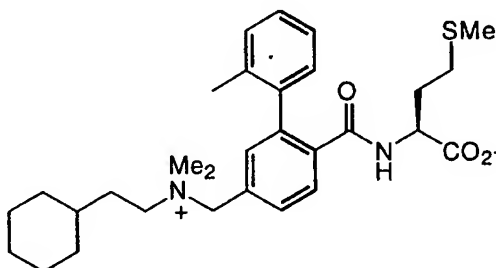
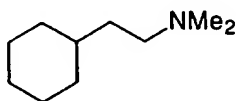
The title compound was prepared according to example 608D, substituting L-norleucine methyl ester•HCl for L-methionine methyl ester•HCl. MS(APCI(+)) 493 (M+H)⁺. MS(APCI(-)) 491 (M-H)⁻.

Example 1060BN-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]norleucine, lithium salt

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]norleucine methyl ester was converted into the title compound according to the procedure in example 608E, and was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 0.62-0.90 (m, 7H), 0.97-1.44 (m, 10H), 1.52-1.64 (m, 5H), 1.95-2.18 (m, 3H), 2.13 (s, 3H), 2.33 (t, J=6 Hz, 2H), 3.48 (s, 2H), 3.56-3.66 (m, 1H), 6.80-6.89 (m, 1H), 7.01-7.22 (m, 5H), 7.30 (d, J=7.8 Hz, 1H), 7.46 (d, J=7.8 Hz, 1H).

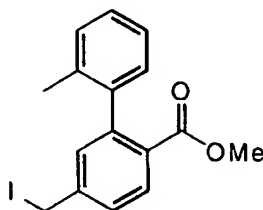
MS (ESI(-)) m/e 477 (M-H); Analysis calc'd for C₃₀H₄₁LiN₂O₃•0.9H₂O: C, 71.95; H, 8.61; N, 5.59; found: C, 72.00; H, 8.36; N, 5.50.

Example 1061N-[4-(N-(2-Cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Internal saltExample 1061AN,N-Dimethyl-2-cyclohexylethylamine

The title compound was prepared from N-methylcyclohexylethylamine (example 608A) according to the procedure described in example 1056A.

¹H NMR (300 MHz, CDCl₃) δ 0.80-0.95 (m, 2H), 1.10-1.39 (m, 6H), 1.60-1.74 (m, 5H), 2.20 (s, 6H), 2.23-2.28 (m, 2H).

MS (DCI/NH₃) m/e 156 (M+H)⁺.

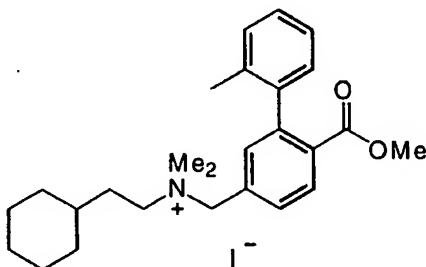


Example 1061B

4-Iodomethyl-2-(2-methylphenyl)benzoic acid, methyl ester

Triphenylphosphine (5.16g), and imidazole (1.34g) were dissolved in 3:1 ether:acetonitrile (80mL), and the reaction was cooled to 0°C. Iodine (5.0g) was added with vigorous stirring, and the reaction was warmed to ambient temperature. After 1h, the reaction was recooled to 0°C and 4-hydroxymethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178C, 4.6g) was added as a solution in ether (20mL). After 4h at ambient temperature, the reaction was diluted with hexane/ether (1:1, 200mL) and filtered. The filtrate was washed with a dilute solution of Na₂SO₃ until colorless, then with water (2X50mL). The organic extracts were washed with brine (20mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexane to give a light yellow oil (4.7g) which slowly crystallizes in the freezer.

¹H NMR (300MHz, CDCl₃) δ 2.06 (s, 3H), 3.60 (s, 3H), 4.45 (AB_q, J_{AB}=9.7Hz, Δν_{AB}=6.7Hz, 2H), 7.03 (brd, J=6.6Hz, 1H), 7.17-7.29 (m, 4H), 7.41 (dd, J=8.1, 1.6Hz, 1H), 7.90 (d, J=8.1Hz, 1H). MS(CI/NH₃) m/e: (M+NH₄)⁺ 384.

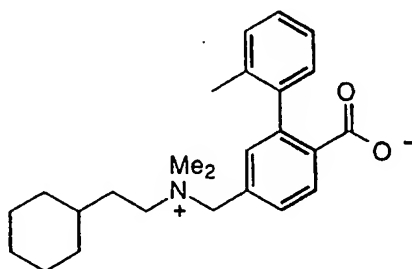


Example 1061C

4-(N-(2-Cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester, Iodide

To a solution of 4-iodomethyl-2-(2-methylphenyl)benzoic acid methyl ester (0.5g) in
 10845 dichloromethane (1mL) was added N,N-dimethyl-2-cyclohexylethylamine (0.233mg), and
 the reaction was stirred at ambient temperature for 2h. The reaction was concentrated to give
 a light yellow foam (760mg, 100%).

¹H NMR (300 MHz, CDCl₃) δ 0.89-1.44 (m, 6H), 1.60-1.73 (m, 7H), 2.06 (s, 3H), 3.34
 (s, 6H), 3.55-3.63 (m, 2H), 3.64 (s, 3H), 5.14 (ABq, Δν_{AB}=56 Hz, J_{AB}=12.7 Hz, 2H),
 10850 7.01 (d, J=7.5 Hz, 1H), 7.17-7.32 (m, 3H), 7.39 (d, J=1.8 Hz, 1H), 7.88 (dd, J=8.1, 1.8
 Hz, 1H), 8.02 (d, J=8.1 Hz, 1H).



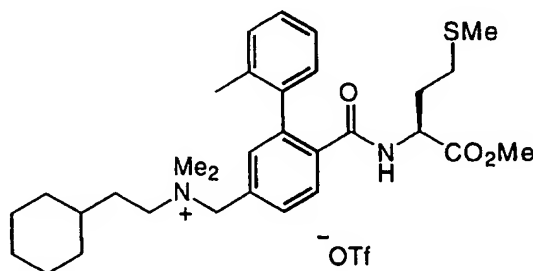
Example 1061D

10855 4-(N-(2-Cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoate, Internal
 salt

To a solution of 4-(N-(2-cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-
 methylphenyl)benzoic acid methyl ester, iodide (700mg) in methanol (3mL) was added 5M
 LiOH (0.54mL). The reaction was refluxed for 1h, then stirred at ambient temperature
 10860 overnight. The reaction was diluted with water (30mL), and purified by preparative reverse-
 phase medium pressure chromatography, eluting with a gradient of methanol/water/TFA
 (0.1%) to give a tan syrup (711mg).

¹H NMR (300 MHz, DMSO) δ 0.90-1.03 (m, 2H), 1.10-1.28 (m, 5H), 1.57-1.73 (m, 6H),
 2.06 (s, 3H), 2.97 (s, 6H), 3.24-3.35 (m, 2H), 4.53-4.57 (m, 2H), 7.07 (d, J=6.9 Hz,
 10865 1H), 7.18-7.30 (m, 3H), 7.43 (d, J=1.5 Hz, 1H), 7.64 (dd, J=8.1, 1.5 Hz, 1H), 7.96 (d,
 J=8.1 Hz, 1H).

MS (ESI) m/e 380 (M+H)⁺.



10870

Example 1061EN-[4-(N-(2-Cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester, Triflate

10875

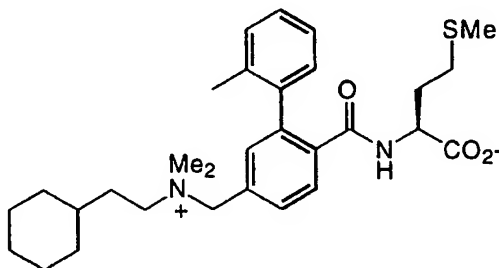
To a solution of 4-(N-(2-cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoate internal salt (771mg) in dichloromethane (5mL) at ambient temperature was added oxalyl chloride (5mL of a 2M solution in CH₂Cl₂). As gas evolution slowed, DMF (5 drops) was added. After stirring at ambient temperature for 20min, the reaction was warmed to reflux for 2h, then cooled, and the solvent was removed under a stream of dry nitrogen to give a tan solid. To a solution of the acid chloride dissolved in dry dichloromethane (10mL) at 0°C was added triethylamine (0.47mL), and L-methionine methyl ester·HCl (320mg). After stirring at ambient temperature overnight, the reaction was concentrated, dissolved in 1:1 methanol/water (30mL), and purified by preparative reverse-phase medium pressure chromatography, eluting with a gradient of methanol/water/TFA (0.1%) to give a tan foam (330mg).

10880

10885

¹H NMR (300 MHz, CDCl₃) δ 0.88-1.40 (m, 7H), 1.60-1.76 (m, 6H), 1.82-1.95 (m, 2H), 2.00-2.19 (m, 8H), 3.21 (brs, 6H), 3.29-3.37 (m, 2H), 3.68 (s, 3H), 4.58-4.65 (m, 3H), 6.09 (d, J=6 Hz, 1H), 7.13-7.40 (m, 6H), 7.57 (brd, J=7.8 Hz, 1H), 8.00 ("t", J=7.8 Hz, 1H).

MS (ESI(-)) m/e 637 (M-H)⁻, 751 (M+TFA-H)⁻.



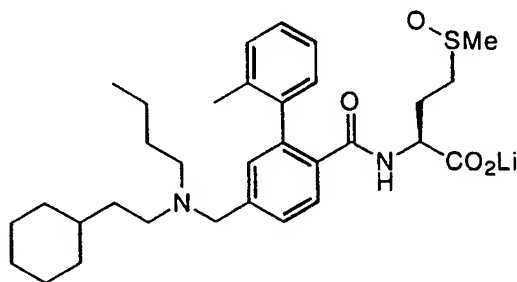
10890

Example 1061FN-[4-(N-(2-Cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Internal salt

10895

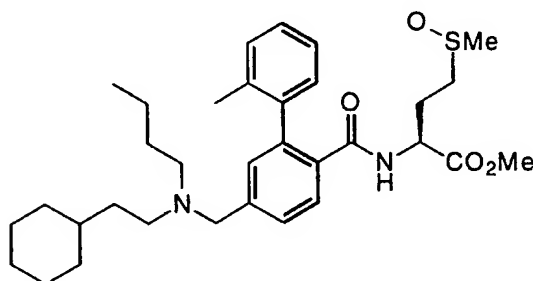
N-[4-(N-(2-Cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester triflate (330mg) was dissolved in methanol (2mL), and 5M LiOH (0.21mL, 2equiv) was added. After stirring at ambient temperature overnight, the reaction was diluted with water (10mL), and purified by preparative reverse-phase medium pressure chromatography, eluting with a gradient of methanol/water/TFA (0.1%) to give a tan powder (168mg) after lyophilization from acetonitrile-water.

- 10900 ^1H NMR (300 MHz, DMSO) δ 0.87-1.04 (m, 2H), 1.08-1.33 (m, 4H), 1.59-1.92 (m, 10H), 1.96 (s, 3H), 2.00-2.24 (m, 4H), 2.97 (brs, 6H), 3.24-3.35 (m, 2H), 4.20-4.30 (m, 1H), 4.56 (brs, 2H), 7.13-7.27 (m, 5H), 7.43 (brs, 1H), 7.62 (brs, 2H), 8.30 (brd, $J=5$ Hz, 1H).
MS (ESI(+)) m/e 511 (M+H); Analysis calc'd for $\text{C}_{30}\text{H}_{42}\text{N}_2\text{O}_3\text{S}\cdot 0.65\text{H}_2\text{O}\cdot 1.30\text{TFA}$: C, 58.38; H, 6.70; N, 4.18; found: C, 58.35; H, 6.67; N, 4.26.



Example 1062

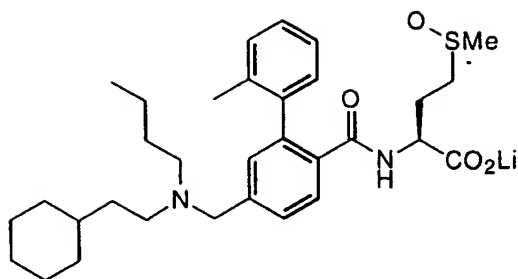
- 10910 (2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt



Example 1062A

- 10915 (2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, Methyl Ester

- To a solution of N-[4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester (example 1178I, 90mg) in dichloromethane (1mL) at 0°C was added trifluoroacetic acid (0.023mL), then 30% hydrogen peroxide (0.05mL). After 2h, the reaction was quenched by addition of sodium sulfite (100mg). The reaction was filtered, concentrated, and the residue was purified by silica gel chromatography eluting with 2.5%-5.0% methanol/dichloromethane to give the title compound as a colorless oil (75mg, 79%). MS(APCI(+)) 569 (M+H)⁺. MS(APCI(-)) 603 (M+Cl)⁻.



10925

Example 1062B

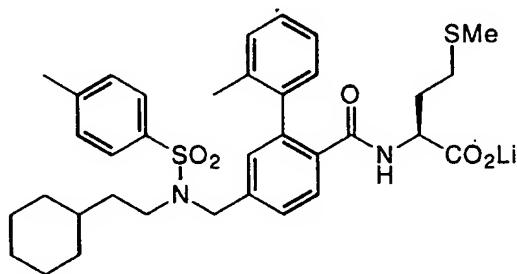
(2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt

10930 (2S) 2-N-[4-(N-(2-Cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate methyl ester was converted to the title compound according to the procedure in example 608E, with the exception that the product was isolated as a colorless foam after trituration with dichloromethane and removal of the solvent under reduced pressure.

10935 ¹H NMR (300 MHz, DMSO) δ 0.76-0.87 (m, 5H), 1.02-1.44 (m, 9H), 1.52-1.88 (m, 8H), 1.92-2.24 (m, 6H), 2.33-2.43 (m, 6H), 3.54 (brs, 2H), 3.64-3.75 (m, 1H), 6.97 (brd, J=5.1 Hz, 1H), 7.06-7.25 (m, 5H), 7.32 (brd, J=7.5 Hz, 1H), 7.49 (d, J=7.5 Hz, 0.5H), 7.51 (d, J=7.5 Hz, 0.5H).

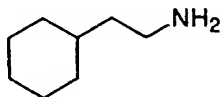
MS (ESI(-)) m/e 553 (M-H).

10940

Example 1063

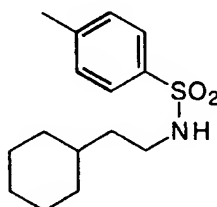
N-[4-(N-(2-Cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

10945

Example 1063A

2-Cyclohexylethylamine

Phenethylamine (50g) was dissolved in 1000mL of glacial acetic acid in a pressure vessel, followed by addition of platinum oxide (15g). After shaking under 4atm of hydrogen for 48h, the reaction was filtered and the acetic acid was removed under reduced pressure. The residue was taken up in water (1000mL), basified with 5N NaOH, and washed with ether (5X250mL). The ether extracts were washed with brine (250mL), dried (MgSO₄), filtered and concentrated to afford a light yellow oil which was purified by fractional distillation at atmospheric pressure (bp 185°C, 49.5g, 94%).
¹H NMR(CDCl₃, 300MHz) δ 0.83-0.95 (m, 2H), 1.00-1.38 (m, 8H), 1.60-1.73 (m, 5H), 2.71 (dd, J=8.1, 7.2Hz, 2H).

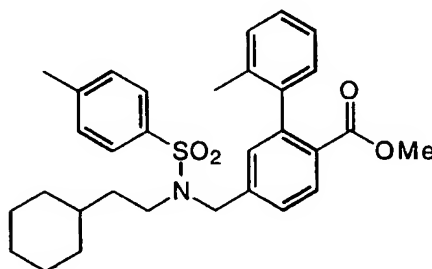


10960

Example 1063BN-2-Cyclohexylethyl-p-toluenesulfonamide

To a solution of p-toluenesulfonyl chloride (210mg), and diisopropylethylamine (0.35mL) in dichloroethane (3mL) was added 2-cyclohexylethylamine (0.15mL, 1.0mmol). After 6h, the reaction was diluted with 1:1 EtOAc/hexane (25mL), washed with water (5mL), 1M HCl (2X5mL) and brine (5mL). The organic solution was dried (MgSO₄), filtered and concentrated to afford a colorless crystalline solid (300mg).
¹H NMR (300 MHz, CDCl₃) δ 0.75-0.91 (m, 2H), 1.06-1.27 (m, 4H), 1.33 (q, J=6.9 Hz, 2H), 1.59-1.70 (m, 5H), 2.43 (s, 3H), 2.95 (q, J=6.9 Hz, 2H), 4.21 (brt, J=5.9 Hz, 1H), 7.31 (d, J=7.8 Hz, 2H), 7.74 (d, J=8.4 Hz, 2H).
 MS (DCI/NH₃) m/e 299 (M+NH₄)⁺.

10970

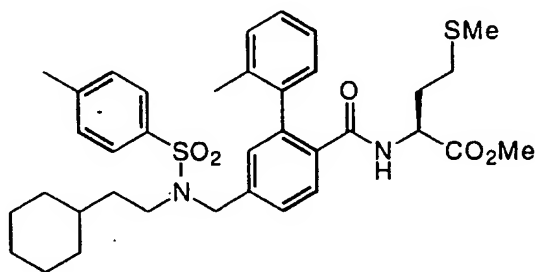
Example 1063C

4-(N-(2-Cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

10975

To a solution of N-2-Cyclohexylethyl-p-toluenesulfonamide (300mg) in DMF (5mL) was added NaH (56mg of a 60% dispersion in mineral oil). After gas evolution subsided, 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester (example 1178D, 266mg) was added. After stirring at ambient temperature for 1.5h, the reaction was quenched by addition of water (10mL), and diluted with 50% EtOAc/hexane (50mL). The organic solution was washed with water (10mL), brine (2X10mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexane to give the title compound as a colorless oil (250mg, 70%).

¹H NMR (300 MHz, CDCl₃) δ 0.64-0.81 (m, 2H), 1.00-1.15 (m, 4H), 1.16-1.27 (m, 2H), 1.42-1.64 (m, 5H), 2.03 (s, 3H), 2.41 (s, 3H), 3.12 (dd, J=9.3, 7.5 Hz, 2H), 3.61 (s, 3H), 4.35 (s, 2H), 7.00 (brd, J=7.2 Hz, 1H), 7.08 (d, J=1.5 Hz, 1H), 7.16-7.27 (m, 3H), 7.28 (d, J=8.1 Hz, 2H), 7.37 (dd, J=8.1, 1.5 Hz, 1H), 7.71 (d, J=8.4 Hz, 2H), 7.42 (d, J=7.1 Hz, 1H).

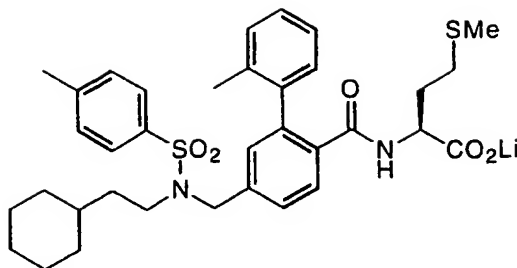


Example 1063D

N-[4-(N-(2-Cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-(2-Cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 0.68-0.82 (m, 2H), 1.00-1.28 (m, 4H), 1.43-1.66 (m, 7H), 1.78-1.92 (m, 2H), 1.98-2.17 (m, 8H), 2.41 (s, 3H), 3.13 (t, J=7.8 Hz, 2H), 3.66 (s, 3H), 4.36 (s, 2H), 4.55-4.67 (m, 1H), 5.88 (brd, J=7.5 Hz, 1H), 7.08-7.37 (m, 8H), 7.71 (d, J=8.4 Hz, 2H), 7.90 ("dd", J=15, 8.4 Hz, 1H). MS(APCI(+)) 651 (M+H)⁺. MS(APCI(-)) 649 (M-H)⁻.

Example 1063E

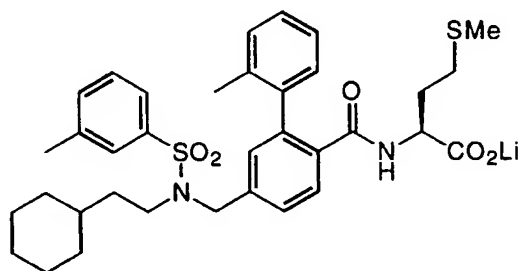
11005 N-[4-(N-(2-Cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(2-Cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder.

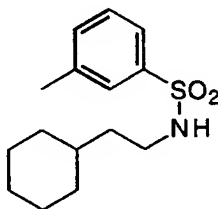
11010 ¹H NMR (300 MHz, DMSO) δ 0.60-0.78 (m, 2H), 0.98-1.20 (m, 6H), 1.38-1.60 (m, 6H), 1.70-1.95 (m, 4H), 1.81 (s, 3H), 1.96-2.18 (m, 3H), 3.03-3.12 (m, 2H), 3.60-3.73 (m, 1H), 4.35 (s, 2H), 6.95 (d, J=6.3 Hz, 1H), 7.0-7.27 (m, 5H), 7.35 (d, J=7.5 Hz, 1H), 7.40 (d, J=8.1 Hz, 2H), 7.50 (d, J=7.8 Hz, 1H), 7.73 (s, J=6.6 Hz, 2H).

MS (APCI(-)) m/e 635 (M-H); Analysis calc'd for C₃₅H₄₃LiN₂O₅S₂•0.80H₂O: C, 63.96;

11015 H, 6.84; N, 4.26; found: C, 63.98; H, 6.68; N, 4.09.

Example 1064

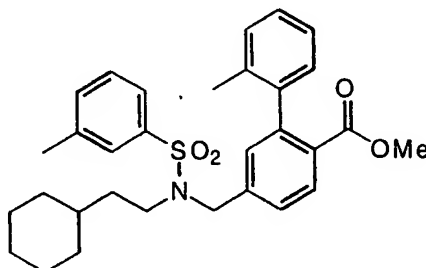
11020 N-[4-(N-(2-Cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

Example 1064A

11025

N-2-Cyclohexylethyl-m-toluenesulfonamide

The title compound was prepared according to example 1063B, replacing p-toluenesulfonyl chloride with m-toluenesulfonyl chloride to afford a colorless oil. MS (DCI/NH₃) m/e 299 (M+NH₄)⁺.



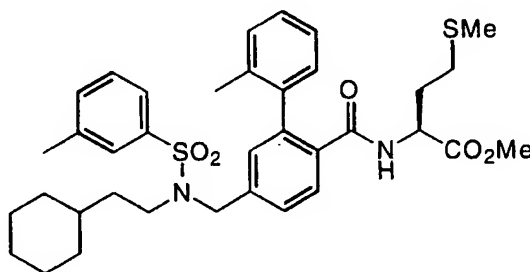
11030

Example 1064B

4-(N-(2-Cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

11035

N-2-Cyclohexylethyl-m-toluenesulfonamide was converted into the title compound according to the procedure in example 1063C to afford a colorless oil. MS (DCI/NH₃) m/e 537 (M+NH₄)⁺.

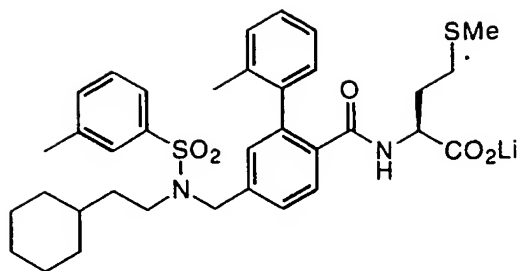
Example 1064C

11040

N-[4-(N-(2-Cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

11045

4-(N-(2-Cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil. MS(APCI(+)) 651 (M+H)⁺. MS(APCI(-)) 649 (M-H)⁻.

Example 1064D

N-[4-(N-(2-Cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

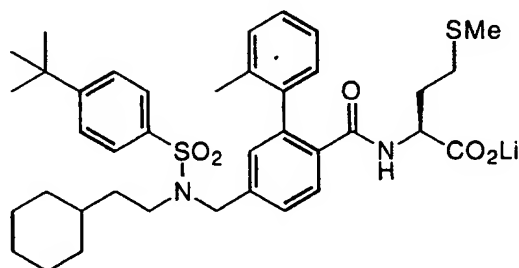
11050

N-[4-(N-(2-Cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder. ¹H NMR (300 MHz, DMSO) δ 0.60-0.77 (m, 2H), 1.00-1.20 (m, 6H), 1.40-1.89 (m, 10H), 1.93 (s, 3H), 1.95-2.14 (m, 3H), 2.39 (s, 3H), 3.05-3.15 (m, 2H), 3.60-3.72 (m, 1H), 4.38 (s, 2H), 6.94 (d, J=5.7 Hz, 1H), 7.02-7.27 (m, 5H), 7.36 (d, J=8.1 Hz, 1H), 7.44-7.54 (m, 3H), 7.60-7.69 (m, 2H).

11055

MS (ESI(-)) m/e 635 (M-H); Analysis calc'd for C₃₅H₄₃LiN₂O₅S₂•1.30H₂O: C, 63.10; H, 6.90; N, 4.20; found: C, 63.06; H, 6.53; N, 4.18.

11060

Example 1065

N-[4-(N-(2-Cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

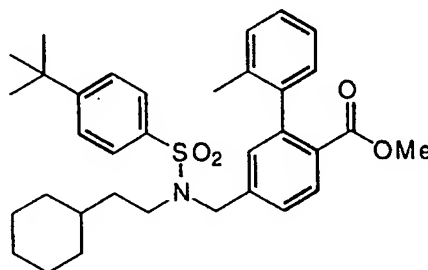
11065



Example 1065AN-2-Cyclohexylethyl-p-tert-butylbenzenesulfonamide

11070 The title compound was prepared according to example 1063B, replacing p-toluenesulfonyl chloride with p-tert-butylbenzenesulfonyl chloride to afford a white crystalline solid.

MS (DCI/NH₃) m/e 341 (M+NH₄)⁺.

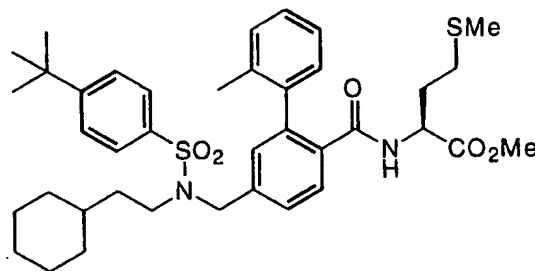


11075

Example 1065B

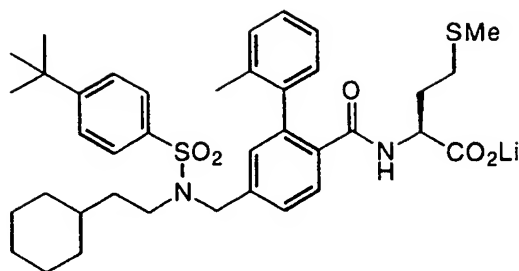
4-(N-(2-Cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

11080 N-2-Cyclohexylethyl-p-tert-butylbenzenesulfonamide (300mg) was converted into the title compound according to the procedure in example 1063C to afford a colorless oil.
MS (DCI/NH₃) m/e 579 (M+NH₄)⁺.

Example 1065C

11085 N-[4-(N-(2-Cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-(2-Cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil. MS(ESI(+)) 693 (M+H)⁺. MS(ESI(-)) 691 (M-H)⁻.
11090

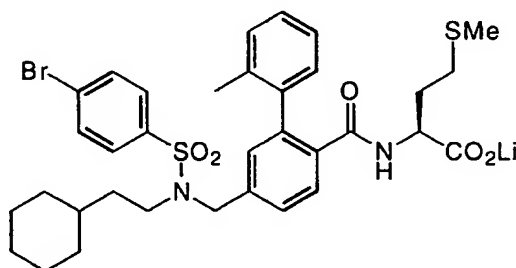


Example 1065D

N-[4-(N-(2-Cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

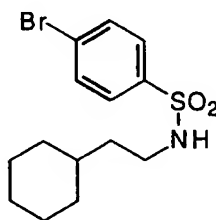
N-[4-(N-(2-Cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder. ¹H NMR (300 MHz, DMSO) δ 0.60-0.75 (m, 2H), 0.96-1.20 (m, 6H), 1.33 (s, 9H), 1.38-1.88 (m, 10H), 1.93 (s, 3H), 1.95-2.18 (m, 3H), 3.04-3.13 (m, 2H), 3.59-3.70 (m, 1H), 4.37 (s, 2H), 6.95 (d, J=5.7 Hz, 1H), 7.10-7.28 (m, 5H), 7.35 (d, J=7.8 Hz, 1H), 7.50 (d, J=6.3 Hz, 1H), 7.63 (d, J=8.4 Hz, 2H), 7.78 (d, J=7.5 Hz, 2H).

MS (ESI(-)) m/e 677 (M-H); Analysis calc'd for C₃₈H₄₉LiN₂O₅S₂•1.55H₂O: C, 64.03; H, 7.37; N, 3.93; found: C, 63.98; H, 7.15; N, 3.92.



Example 1066

N-[4-(N-(2-Cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt



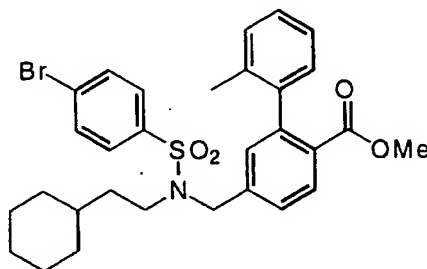
Example 1066A

N-2-Cyclohexylethyl-p-bromobenzenesulfonamide

11115

The title compound was prepared according to example 1063B, replacing p-toluenesulfonyl chloride with p-bromobenzenesulfonyl chloride to afford a white crystalline solid.

MS (DCI/NH₃) m/e 363 (M(⁷⁹Br)+NH₄)⁺, 365 (M(⁸¹Br)+NH₄)⁺.



11120

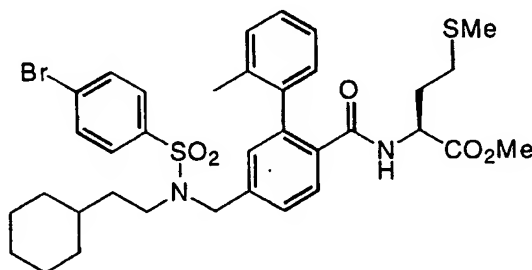
Example 1066B

4-(N-(2-Cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

11125

N-2-Cyclohexylethyl-p-bromobenzenesulfonamide (300mg) was converted into the title compound according to the procedure in example 1063C to afford a colorless oil.

MS (DCI/NH₃) m/e 601 (M(⁷⁹Br)+NH₄)⁺, 603 (M(⁸¹Br)+NH₄)⁺.

Example 1066C

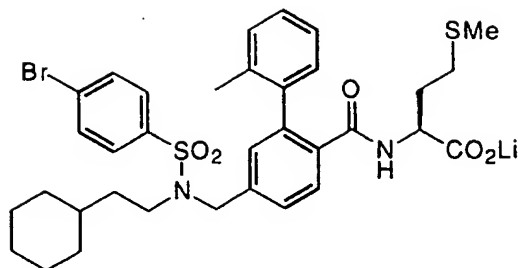
11130

N-[4-(N-(2-Cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-(2-Cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil. MS(APCI(+))

11135

715 (M(⁷⁹Br)+H)⁺, 717 (M(⁸¹Br)+H)⁺. MS(APCI(-)) 749 (M(⁷⁹Br)+Cl)⁻, 751 (M(⁸¹Br)+Cl)⁻.

Example 1066D

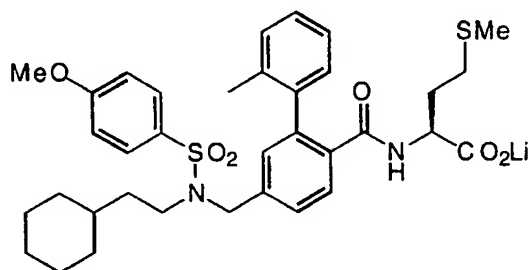
11140 N-[4-(N-(2-Cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(2-Cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder.

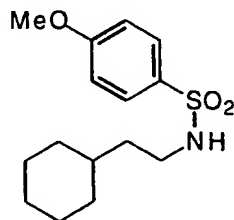
11145 ¹H NMR (300 MHz, DMSO) δ 0.60-0.75 (m, 2H), 0.94-1.21 (m, 6H), 1.38-1.88 (m, 10H), 1.93 (s, 3H), 1.95-2.15 (m, 3H), 3.06-3.15 (m, 2H), 3.55-3.67 (m, 1H), 4.36 (s, 2H), 6.96 (d, J=6 Hz, 1H), 7.03-7.26 (m, 5H), 7.37 (d, J=8.1 Hz, 1H), 7.54 (d, J=8.1 Hz, 1H), 7.76-7.85 (m, 4H).

MS (ESI(-)) m/e 699 (M(⁷⁹Br)+H)⁺, 701 (M(⁸¹Br)+H)⁺; Analysis calc'd for

11150 C₃₄H₄₀BrLiN₂O₅S₂•0.95H₂O: C, 56.34; H, 5.83; N, 3.86; found: C, 56.33; H, 5.66; N, 3.48.

Example 1067

11155 N-[4-(N-(2-Cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

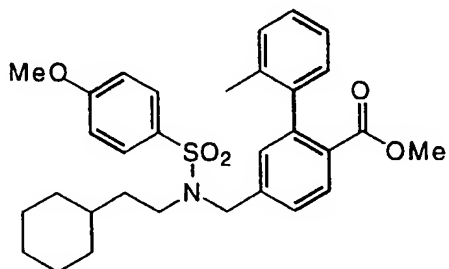


11160

Example 1067AN-2-Cyclohexylethyl-p-methoxybenzenesulfonamide

The title compound was prepared according to example 1063B, replacing p-toluenesulfonyl chloride with p-methoxybenzenesulfonyl chloride to afford a colorless oil. MS (DCI/NH₃) m/e 315 (M+NH₄)⁺.

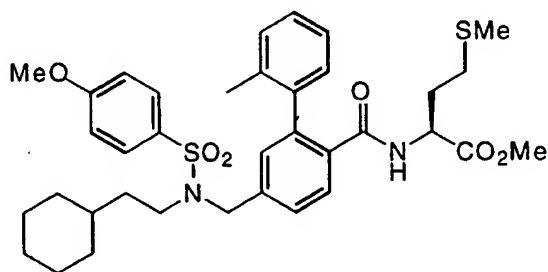
11165

Example 1067B

4-(N-(2-Cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

11170

N-2-Cyclohexylethyl-p-methoxybenzenesulfonamide (300mg) was converted into the title compound according to the procedure in example 1063C to afford a colorless oil. MS (DCI/NH₃) m/e 553 (M+NH₄)⁺.



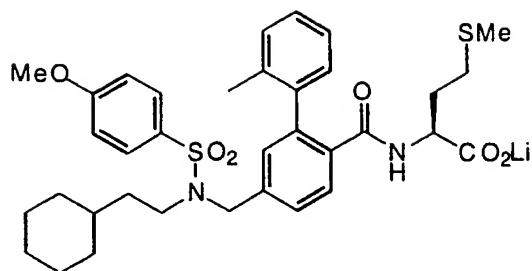
11175

Example 1067C

N-[4-(N-(2-Cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-(2-Cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil. MS(APCI(+)) 667 (M+H)⁺. MS(APCI(-)) 701 (M+Cl)⁻.

11180

Example 1067D

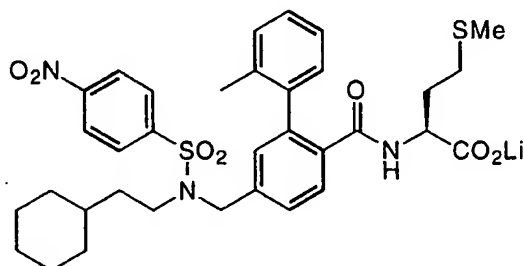
11185 N-[4-(N-(2-Cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(2-Cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder.

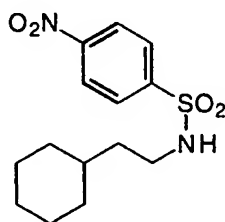
11190 ^1H NMR (300 MHz, DMSO) δ 0.62-0.78 (m, 2H), 1.00-1.22 (m, 6H), 1.37-1.85 (m, 10H), 1.90 (s, 3H), 1.90-2.16 (m, 3H), 3.01-3.10 (m, 2H), 3.58-3.67 (m, 1H), 3.83 (s, 3H), 4.32 (s, 2H), 6.94 (d, $J=6$ Hz, 1H), 7.04-7.26 (m, 5H), 7.11 (d, $J=8.7$ Hz, 2H), 7.35 (dd, $J=8.1$, 1 Hz, 1H), 7.51 (d, $J=8.1$ Hz, 1H), 7.77 (d, $J=8.7$ Hz, 2H).

MS (APCI(-)) m/e 651 (M-H); Analysis calc'd for $\text{C}_{35}\text{H}_{43}\text{LiN}_2\text{O}_6\text{S}_2 \cdot 1.85\text{H}_2\text{O}$: C, 61.35;

11195 H, 6.87; N, 4.09; found: C, 61.36; H, 6.48; N, 3.91.

Example 1068

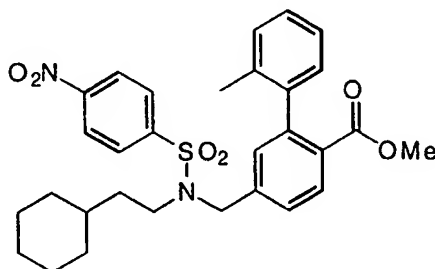
11200 N-[4-(N-(2-Cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Example 1068A

11205

N-2-Cyclohexylethyl-p-nitrobenzenesulfonamide

The title compound was prepared according to example 1063B, replacing p-toluenesulfonyl chloride with p-nitrobenzenesulfonyl chloride to afford a colorless oil. MS (DCI/NH₃) m/e 330 (M+NH₄)⁺.

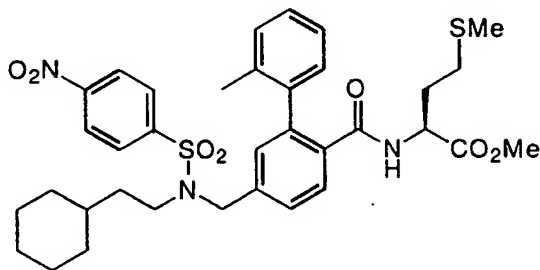


11210

Example 1068B

4-(N-(2-Cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

11215 N-2-Cyclohexylethyl-p-nitrobenzenesulfonamide (300mg) was converted into the title compound according to the procedure in example 1063C to afford a colorless oil. MS (DCI/NH₃) m/e 568 (M+NH₄)⁺.

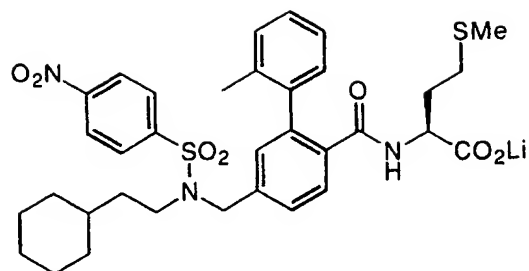
Example 1068C

11220

N-[4-(N-(2-Cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-(2-Cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil. MS(APCI(+)) 682 (M+H)⁺. MS(APCI(-)) 716 (M+Cl)⁻.

11225

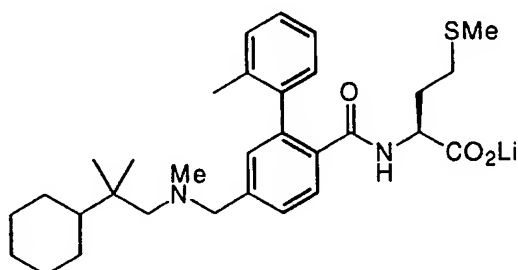
Example 1068D

N-[4-(N-(2-Cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

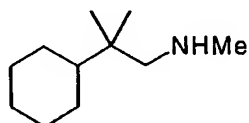
N-[4-(N-(2-Cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 0.63-0.76 (m, 2H), 1.00-1.26 (m, 6H), 1.40-1.70 (m, 10H), 1.92 (s, 3H), 1.95-2.15 (m, 3H), 3.12-3.20 (m, 2H), 3.59-3.65 (m, 1H), 4.43 (s, 2H), 6.96 (d, J=6.3 Hz, 1H), 7.0-7.25 (m, 5H), 7.36 (d, J=8.1 Hz, 1H), 7.52 (d, J=7.8 Hz, 1H), 8.13 (d, J=8.7 Hz, 2H), 8.37 (d, J=8.4 Hz, 2H).

MS (APCI(-)) m/e 667 (M⁻); Analysis calc'd for C₃₄H₄₀LiN₃O₇S₂•1.2H₂O: C, 58.73; H, 6.15; N, 6.04; found: C, 58.73; H, 5.82; N, 5.92.

Example 1069

N-[4-(N-(2-Cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

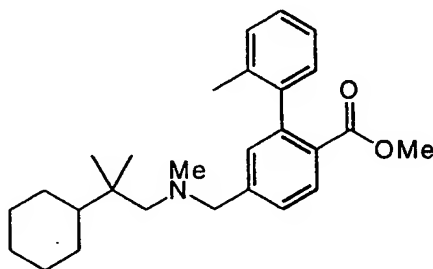
Example 1069A

N-Methyl-2-cyclohexyl-2-methylpropylamine

Treatment of 2-phenyl-2-methylpropylamine (example 1048A, 5g) with di-tert-butylidicarbonate according to example 1056A afforded N-tert-butoxycarbonyl-2-phenyl-2-methylpropylamine (10g crude) as a colorless oil. To portion of this material (5g) in methanol (100mL) was added platinum oxide (1g), and the reaction was shaken under hydrogen gas (4atm) for 24h. The reaction was concentrated, diluted with water (100mL), and extracted with chloroform (3X50mL). The organic extracts were washed with brine (20mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexane to afford a colorless oil (1.0g). This material was reduced with LiAlH₄ according to the procedure described in example 1056A to afford the title compound (0.8g), as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 0.83 (s, 6H), 0.87-1.29 (m, 6H), 1.60-1.82 (m, 5H), 2.36 (s, 2H), 2.42 (s, 3H).

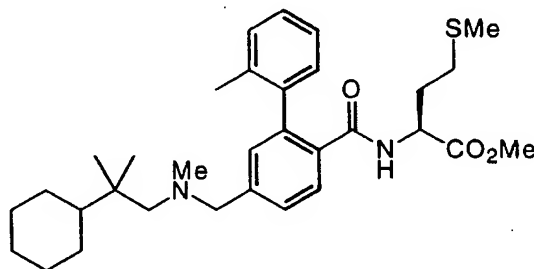
MS (APCI(+)) m/e 170 (M+H)⁺.



Example 1069B

4-(N-(2-Cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

The title compound was prepared according to the procedure in example 608B, substituting N-methyl-2-cyclohexyl-2-methylpropylamine for N-methylcyclohexylethylamine, and was isolated as a colorless oil. MS(ESI(+)) m/e 408 (M+H)⁺.

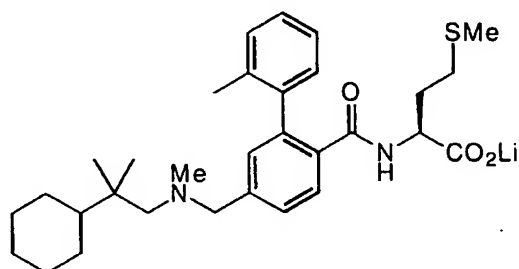


Example 1069C

11275 N-[4-(N-(2-Cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

The title compound was prepared from 4-(N-(2-cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester according to the procedures described in examples 608C, and D, and was isolated as a colorless oil.

11280 MS(ESI(+)) m/e 539 (M+H)⁺. MS(ESI(-)) m/e 537 (M-H)⁻.



Example 1069D

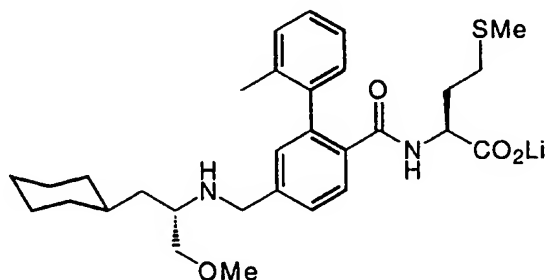
11285 N-[4-(N-(2-Cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

The title compound was prepared from N-[4-(N-(2-cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester according to the procedure in example 608E, and was isolated as a white powder.

11290 ¹H NMR (300 MHz, DMSO) δ 0.79 (s, 6H), 0.80-1.27 (m, 5H), 1.50-1.74 (m, 6H), 1.75-2.95 (m, 7H), 1.92 (s, 3H), 2.19 (s, 3H), 2.24 (s, 2H), 3.56 (s, 2H), 3.62-3.72 (m, 1H), 6.92 (d, J=6 Hz, 1H), 7.08-7.25 (m, 5H); 7.36 (d, J=7.8 Hz, 1H), 7.49 (d, J=7.8 Hz, 1H).

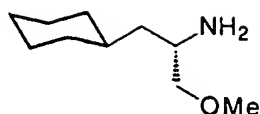
MS (ESI(-)) m/e 523 (M-H); Analysis calc'd for C₃₁H₄₃LiN₂O₃S•1.3H₂O: C, 67.70; H, 8.29; N, 5.06; found: C, 67.15; H, 8.08; N, 4.97.

11295



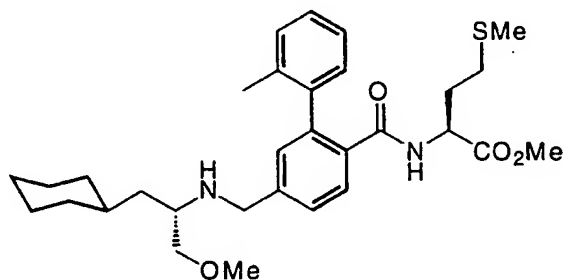
Example 1070

11300 N-[4-(3-Cyclohexyl-1-methoxyprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Example 1070A(S)-3-Cyclohexyl-1-methoxy-2-propylamine

11305 To a solution of (S)-3-phenyl-1-methoxy-2-propylamine hydrochloride (0.5g) in ethanol (100ml) was added concentrated HCl (0.32mL), and platinum oxide (0.5g), and the reaction was shaken under hydrogen gas (4atm) for 18h. The reaction was filtered, concentrated, diluted with water (50mL) and neutralized with 1M NaOH (to pH≈11). The mixture was washed with chloroform (3X50mL), and the organic extracts were washed
11310 with brine (20mL), dried (MgSO₄), filtered and concentrated to give a colorless oil (400mg).

¹H NMR (300 MHz, CDCl₃) δ 0.76-1.00 (m, 2H), 1.10-1.48 (m, 6H), 1.61-1.81 (m, 5H), 3.01-3.14 (m, 2H), 3.30-3.35 (m, 1H), 3.36 (s, 3H).



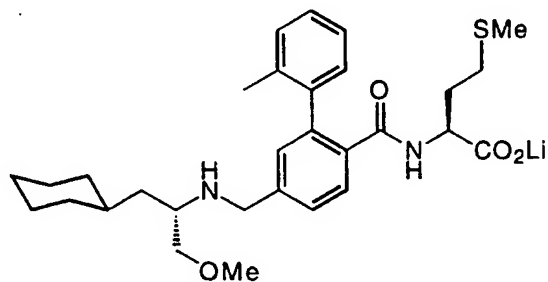
11315

Example 1070B

N-[4-(3-Cyclohexyl-1-methoxyprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

11320 The title compound was prepared from (S)-3-cyclohexyl-1-methoxy-2-propylamine according to the procedure described in example 403H to afford a colorless oil.

MS(APCI(+)) 541 (M+H)⁺. MS(APCI(-)) 539 (M-H)⁻.

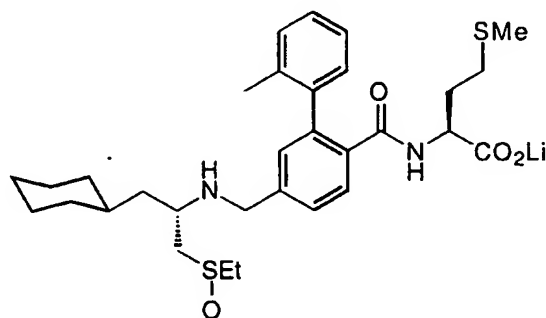
Example 1070C

11325 N-[4-(3-Cyclohexyl-1-methoxyprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(3-Cyclohexyl-1-methoxyprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted into the title compound according to the procedure described in example 608E, affording a white powder.

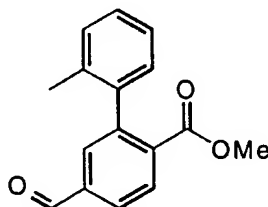
11330 ^1H NMR (300 MHz, DMSO) δ 0.65-0.88 (m, 2H), 1.00-1.88 (m, 15H), 1.91 (s, 3H), 1.95-2.19 (m, 3H), 2.61-2.68 (m, 1H), 3.20 (s, 3H), 3.20-3.26 (m, 2H), 3.62-3.84 (m, 3H), 6.85-7.00 (m, 2H), 7.09-7.24 (m, 5H), 7.36 (d, $J=7.8$ Hz, 1H), 7.48 (d, $J=7.8$ Hz, 1H).

MS (APCI(-)) m/e 525 (M-H); Analysis calc'd for $\text{C}_{30}\text{H}_{41}\text{LiN}_2\text{O}_4\text{S}\cdot 0.60\text{H}_2\text{O}$: C, 66.30; H, 7.83; N, 5.15; found: C, 66.29; H, 7.69; N, 5.15.



Example 1071

11340 N-[4-(1-Ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt



Example 1071A

11345 4-Formyl-2-(2-methylphenyl)benzoic acid methyl ester

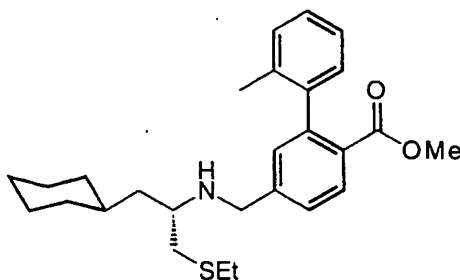
To a solution of 4-hydroxymethyl-2-(2-methylphenyl)benzoic acid methyl ester (example 1178C, 1.0g) in dichloromethane (10mL) was added infusorial earth (2g) then at 0°C was added pyridinium chlorochromate (1.7g). After 10min, the reaction was warmed to ambient temperature. After 1h, the reaction was diluted with ether (50mL), and filtered through infusorial earth. The solution was concentrated, and the residue was purified by

11350

silica gel chromatography eluting with 20% EtOAc/hexanes to afford the title compound as a colorless oil (0.842g, 85%).

^1H NMR (300 MHz, CDCl_3) δ 2.08 (s, 3H), 3.63 (s, 3H), 7.07 (brd, $J=6.6$ Hz, 1H), 7.19-7.30 (m, 3H), 7.76 (d, $J=1.8$ Hz, 1H), 7.93 (dd, $J=8.1, 1.6$ Hz, 1H), 8.06 (d, $J=8.1$ Hz, 1H), 10.09 (s, 1H).

MS (DCI/ NH_3) m/e 255 ($\text{M}+\text{H}$) $^+$.

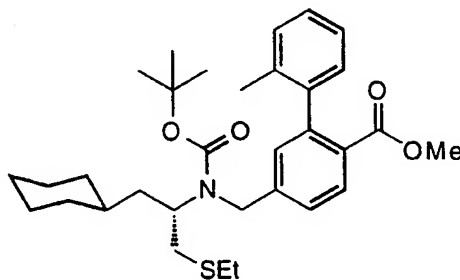


Example 1071B

4-N-(3-Cyclohexyl-1-ethylthioprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoic acid, Methyl Ester

The title compound was prepared according to example 403H, substituting 4-formyl-2-(2-methylphenyl)benzoic acid methyl ester for N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, to afford a colorless oil in 70% yield.

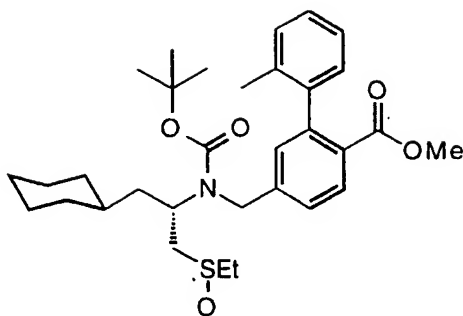
MS(APCI(+)) 440 ($\text{M}+\text{H}$) $^+$. MS(APCI(-)) 438 ($\text{M}-\text{H}$) $^-$.



Example 1071C

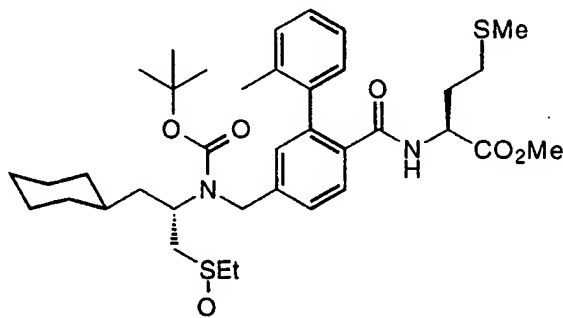
4-N-tert-Butoxycarbonyl-N-(3-cyclohexyl-1-ethylthioprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoic acid, Methyl Ester

To a solution of 4-N-(3-cyclohexyl-1-ethylthioprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoic acid methyl ester (497mg) in dichloromethane (4mL) was added di-tert-butylidicarbonate (300mg). After 16h at ambient temperature, the reaction was concentrated, and the residue was purified by silica gel chromatography eluting with 10% EtOAc/hexane to give the title compound as a colorless oil (605mg). MS(APCI(-)) 538 ($\text{M}-\text{H}$) $^-$.

**Example 1071D**

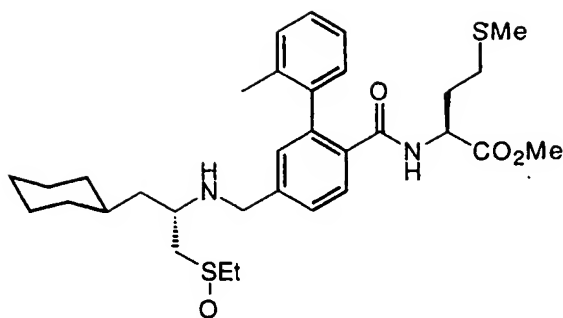
11380 4-N-tert-Butoxycarbonyl-N-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

To a solution of 4-N-tert-Butoxycarbonyl-N-(3-cyclohexyl-1-ethylthioprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoic acid methyl ester (600mg) in dichloromethane (5mL) at -78°C was added m-chloroperbenzoic acid (280mg@75%). After 1.5h, the
 11385 reaction was warmed to 0°C, and after 30min, the reaction was quenched with dilute aqueous sodium sulfite. The product was extracted into EtOAc (30mL), and washed with sodium bicarbonate (3X5mL). The organic extracts were washed with brine (10mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography eluting with 50%-100% EtOAc/hexane to afford a white foam (460mg, 75%). MS(APCI(+))
 11390 556 (M+H)⁺. MS(APCI(-)) 590 (M+Cl)⁻.

**Example 1071E**

11395 N-tert-Butoxycarbonyl-N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

The title compound was prepared from 4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester according to the procedure described in examples 608C and D to afford a colorless oil which was purified by silica gel chromatography eluting with 5% methanol/dichloromethane. MS(APCI(+)) 687 (M+H)⁺.
 11400 MS(APCI(-)) 721 (M+Cl)⁻.

Example 1071F

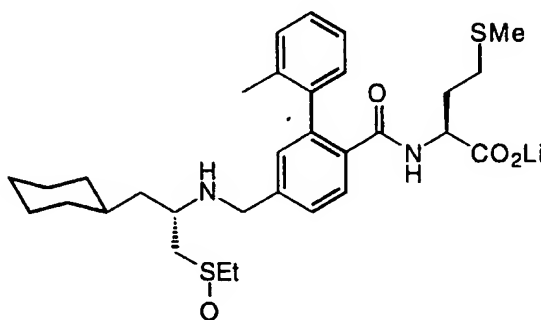
N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, Methyl Ester

11405

To a solution of N-tert-butoxycarbonyl-N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester (200mg) in dioxane (1mL) chilled to its melting point, was added HCl (0.75mL, 4M in dioxane). After 1h, the reaction was quenched with excess aqueous sodium bicarbonate, and extracted into

11410

dichloromethane. The solution was concentrated, and the residue was purified by silica gel chromatography eluting with 5% methanol/dichloromethane to afford the title compound as a colorless oil (72mg, 42%). MS(APCI(+)) 587 (M+H)⁺. MS(APCI(-)) 621 (M+Cl)⁻.

Example 1071G

N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

11415

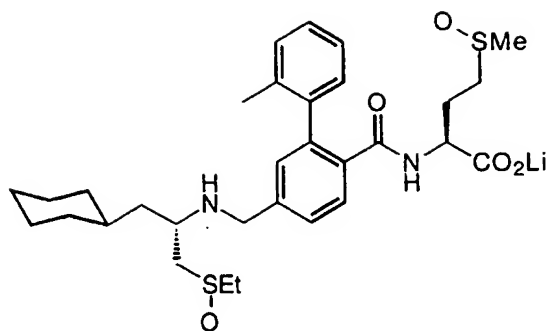
N-[4-(1-Ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted into the title compound

11420

according to the procedure described in example 608E.

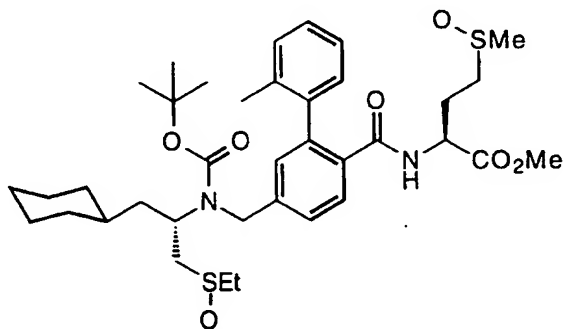
¹H NMR (300 MHz, DMSO) δ 0.67-0.93 (m, 2H), 1.00-1.90 (m, 13H), 1.11 (t, J=7.5 Hz, 3H), 1.94-2.20 (m, 6H), 2.34-2.45 (m, 5H), 2.56-2.67 (m, 2H), 3.62-3.83 (m, 3H), 6.98 (brd, J=6 Hz, 1H), 7.10-7.24 (m, 5H), 7.38 (brd, J=7.8 Hz, 1H), 7.49 (d, J=7.8 Hz, 0.5H), 7.5 (d, J=7.8 Hz, 0.5H).

11425 MS (ESI(-)) m/e 571 (M-H).



Example 1072

11430 (2S) 2-N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt



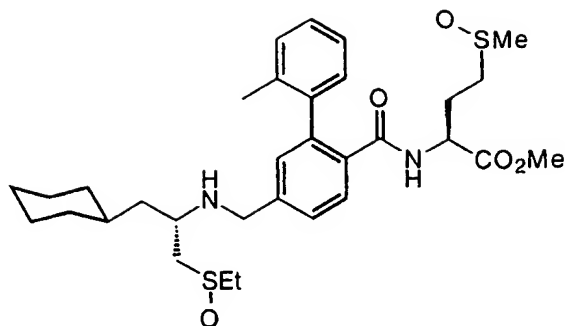
Example 1072A

11435 (2S) N-tert-Butoxycarbonyl-2-N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, Methyl Ester

To a solution of N-tert-butoxycarbonyl-N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester (example 1071E, 320mg) in dichloromethane (2mL) at -78°C was added m-chloroperbenzoic acid

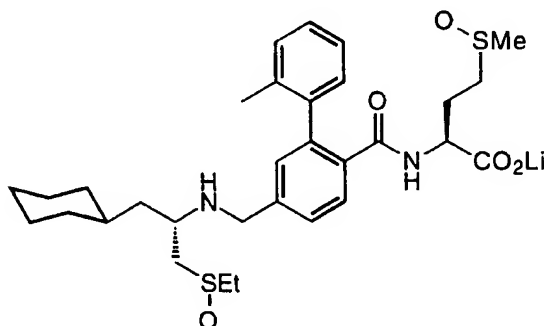
11440 (120mg@75%). After 1.5h, the reaction was warmed to -50°C, and after 30min, the reaction was quenched with dilute aqueous sodium sulfite. The product was extracted into EtOAc (30mL), and washed with sodium bicarbonate (3X5mL). The organic extracts were washed with brine (10mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography eluting with 5% methanol/dichloromethane to afford a

11445 white foam (311mg, 95%). MS(APCI(+)) 703 (M+H)⁺. MS(APCI(-)) 737 (M+Cl)⁻.

Example 1072B

(2S) 2-N-[4-(1-Ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, Methyl Ester

The title compound was prepared from (2S) N-tert-butoxycarbonyl-2-N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate methyl ester according to the procedure described in example 1071F in 58% yield. The product was purified by silica gel chromatography eluting with 5%-10% methanol/dichloromethane, and was isolated as a white foam. MS(APCI(+)) 603 (M+H)⁺. MS(APCI(-)) 637 (M+Cl)⁻.

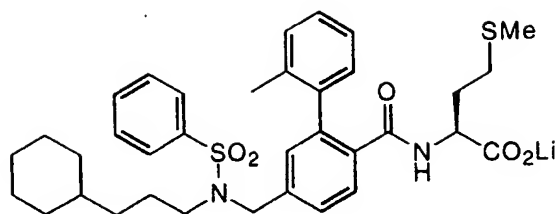
Example 1072C

(2S) 2-N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt

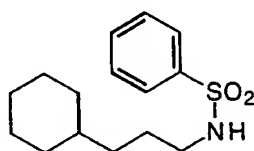
(2S) 2-N-[4-(1-Ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate methyl ester was converted into the title compound according to the procedure described in example 608E, and was isolated as a yellow powder.

¹H NMR (300 MHz, DMSO) δ 0.72-0.90 (m, 2H), 1.03-1.20 (m, 5H), 1.20-1.90 (m, 11H), 1.94-2.23 (m, 5H), 2.36 (s, 3H), 2.57-2.80 (m, 4H), 2.98 (brs, 1H), 3.64-3.82 (m, 3H), 6.95-7.00 (m, 1H), 7.09-7.23 (m, 5H), 7.33-7.41 (m, 1H), 7.49 (d, J=8.1 Hz, 0.5H), 7.50 (d, J=8.1 Hz, 0.5H).

MS (ESI(-)) m/e 587 (M-H).

Example 1073

11475 N-[4-(N-(3-cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

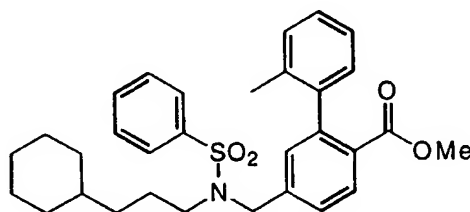
Example 1073A

11480 N-3-Cyclohexylpropylbenzenesulfonamide

The title compound was prepared according to example 1063A (replacing phenethylamine with 3-phenylpropylamine, and example 1063B, replacing p-toluenesulfonyl chloride with benzenesulfonyl chloride to afford a colorless oil.

MS (DCI/NH₃) m/e 299 (M+NH₄)⁺.

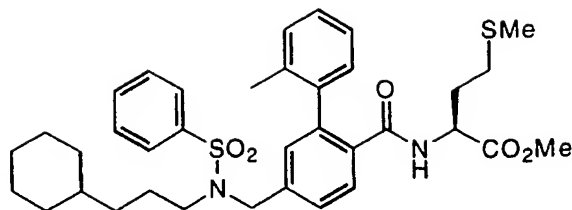
11485

Example 1073B

4-(N-(3-cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

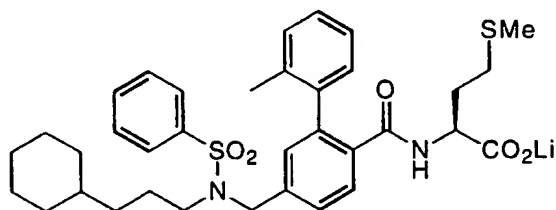
11490 N-3-Cyclohexylpropylbenzenesulfonamide was converted into the title compound according to the procedure in example 1063C to afford a colorless oil.

MS (DCI/NH₃) m/e 537 (M+NH₄)⁺.

Example 1073C

N-[4-(N-(3-cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

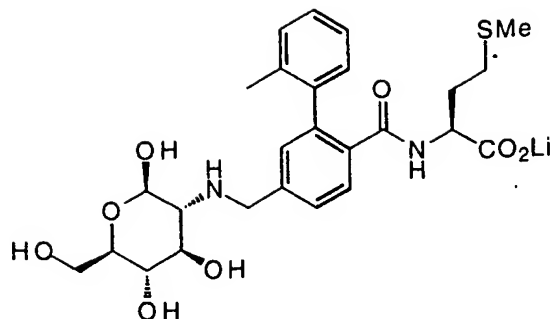
4-(N-(3-Cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted into the title compound according to the procedures described in examples 608C and D to afford a colorless oil. MS(ESI(+)) 651 (M+H)⁺. MS(ESI(-)) 649 (M-H)⁻.

Example 1073D

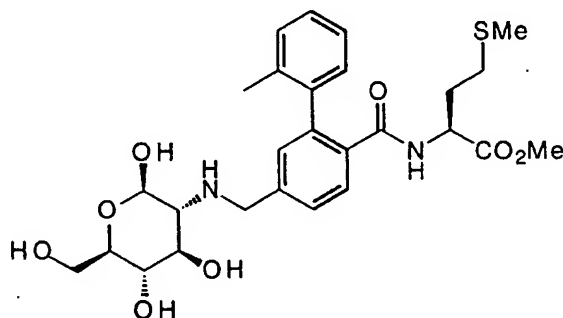
N-[4-(N-(3-cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(3-Cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound according to the procedure described in example 608E, and was isolated as a white powder. ¹H NMR (300 MHz, DMSO) δ 0.59-0.73 (m, 2H), 0.88-1.88 (m, 17H), 1.94 (s, 3H), 1.95-2.16 (m, 3H), 3.00-3.08 (m, 2H), 3.59-3.68 (m, 1H), 4.39 (s, 2H), 6.96 (d, J=6 Hz, 1H), 7.04-7.28 (m, 5H), 7.36 (d, J=7.8 Hz, 1H), 7.51 (d, J=7.8 Hz, 1H), 7.56-7.70 (m, 3H), 7.85 (d, J=6.9 Hz, 2H).

MS (ESI(-)) m/e 635 (M-H); Analysis calc'd for C₃₅H₄₃LiN₂O₅S₂•1.65H₂O: C, 62.51; H, 6.94; N, 4.17; found: C, 62.48; H, 6.79; N, 4.07.

Example 1074

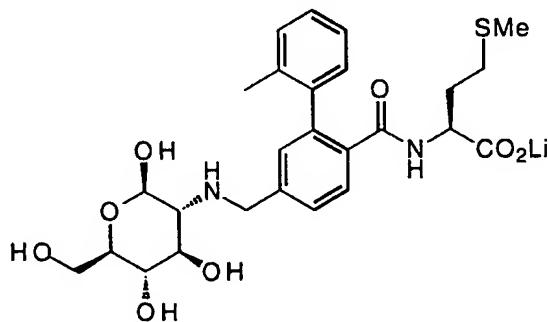
11520

N-[4-(N-glucosaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium saltExample 1074AN-[4-(N-glucosaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

11525

A 1M solution of glucosamine was prepared by dissolving glucosamine•HCl (10g) in 1M NaOH (47mL). This solution (0.311mL) was added to N-[4-formyl-2-(2-methylphenyl)benzoyl] methionine methyl ester (example 403G, 100mg), in ethanol (3mL). Once dissolution was complete, the reaction was degassed, and 10% palladium on carbon (330mg) was added, followed by blanketing the reaction with a hydrogen atmosphere (1atm). After 4h, the reaction was filtered and concentrated, and the residue was purified by silica gel chromatography eluting with 20% methanol/dichloromethane to give the title compound as a colorless syrup (50mg, 35%). MS(ESI(+)) 549 (M+H)⁺, 571 (M+Na)⁺.

11530

Example 1074B

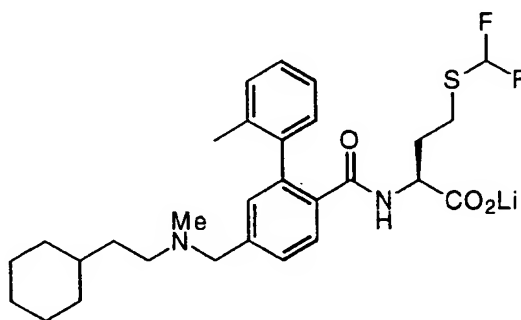
11535

N-[4-(N-glucosaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

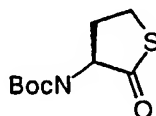
The title compound was prepared from N-[4-(N-Glucosaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester according to the procedure described in example 608E, and was isolated as a fluffy white powder.

11540 ¹H NMR (300 MHz, CD₃OD) δ 1.60-1.90 (m, 4H), 1.95-2.09 (m, 6H), 2.26 (brs, 2H), 2.41 (brt, J=9.3 Hz, 1H), 2.54 (dd, J=10.2, 3.3 Hz, 1H), 3.22-3.30 (m, 2H), 3.58-4.03 (m, 5H), 4.13-4.28 (m, 2H), 4.58 (d, J=7.8 Hz, 1H), 5.17-5.22 (m, 1H), 7.07-7.30 (m, 6H), 7.42-7.47 (m, 1H), 7.61-7.67 (m, 1H).
MS (ESI(-)) m/e 533 (M-H).

11545

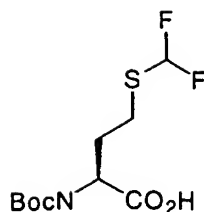
Example 1079

11550 (2S)-2-N-[4-(N-2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-difluoromethylthiobutanoate, lithium salt

Example 1079AN-tert-Butoxycarbonylhomocysteine thiolactone

11555 To a solution of L-homocysteinethiolactone hydrochloride (560mg) in dioxane (10mL) was added triethylamine (0.6mL), and di-tert-butyl dicarbonate (874mg). After 20h, the reaction was diluted with EtOAc (100mL), washed with water (20mL), 1M HCl (20mL), and again with water (2X20mL). The organic extracts were washed with brine (20mL), dried (MgSO₄), filtered and concentrated to give a white crystalline solid.

11560 ¹H NMR (300 MHz, CDCl₃) δ 1.45 (s, 9H), 1.97 (ddd, J=25, 11.7, 6.6 Hz, 1H), 2.86 (m, 1H), 3.23 (dd, J=11.4, 1.5 Hz, 1H), 3.32 (ddd, J=11.4, 11.4, 5.1 Hz, 1H), 4.28 (m, 1H), 4.98 (brs, 1H).

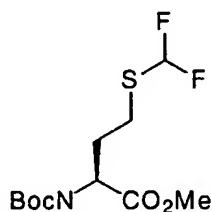
Example 1079BN-tert-Butoxycarbonyl-S-difluoromethylhomocysteine

To a solution of N-tert-butoxycarbonylhomocysteine thiolactone hydrochloride (400mg) in THF (2mL) at 0°C was added 1M NaOH (6mL). After stirring for 20min, this solution was added to chlorodifluoromethane (≈ 0.25 mL) at -78°C in a pressure tube. The vessel was sealed, and warmed to 60°C for 14h. The reaction was chilled to -78°C, opened, and warmed to ambient temperature. The aqueous solution was neutralized with 1M HCl, and extracted into dichloromethane (30mL). The organic extracts were washed with brine (20mL), dried (MgSO₄), filtered and concentrated to give the title compound as a syrup (490mg).

¹H NMR (300 MHz, CDCl₃) δ 1.45 (s, 9H), 1.95-2.36 (m, 2H), 2.63 (q, J=7.4 Hz, 1H), 2.90 (ddd, J=7.6, 7.6, 2.7 Hz, 1H), 4.46 (brs, 1H), 5.05 (brs, 1H), 6.82 (t, J=56 Hz, 1H).

MS (ESI(+)) m/e 308 (M+Na)⁺.

MS (ESI(-)) m/e 285 (M-H)⁻.

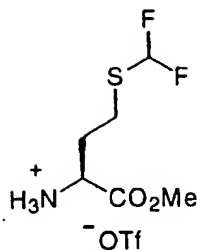
Example 1079CN-tert-Butoxycarbonyl-S-difluoromethylhomocysteine, Methyl Ester

To a solution of N-tert-butoxycarbonyl-S-difluoromethylhomocysteine in diethyl ether (1mL) was added a solution of diazomethane in ether until a faint yellow color persisted. The excess reagent was quenched by addition of glacial acetic acid, and the reaction was concentrated. The residue was purified by silica gel chromatography eluting with 20% EtOAc/hexane to afford a colorless oil (400mg).

¹H NMR (300 MHz, CDCl₃) δ 1.45 (s, 9H), 1.90-2.30 (m, 2H), 2.85 (t, J=7.5 Hz, 2H), 3.77 (s, 3H), 4.42 (brs, 1H), 5.08 (brs, 1H), 6.81 (t, J=56.1 Hz, 1H).

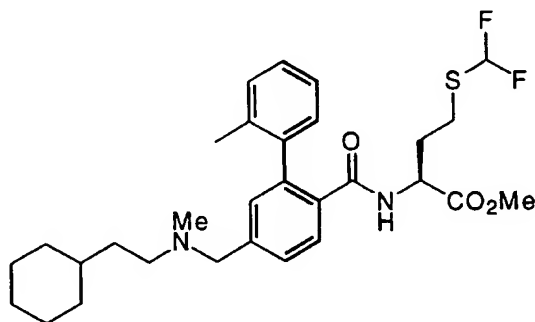
MS (ESI(+)) m/e 322 (M+Na)⁺.

MS (ESI(-)) m/e 298 (M-H)⁻.

Example 1079DS-difluoromethylhomocysteine, Methyl Ester, Trifluoroacetate

To a solution of N-tert-butoxycarbonyl-S-difluoromethylhomocysteine methyl ester (400mg) in dichloromethane (2mL) was added trifluoroacetic acid (1mL). After stirring 18h at ambient temperature, the reaction was concentrated, and the residue was triturated with

toluene and evaporated to give the title compound as a tan solid (515mg).
¹H NMR (300 MHz, CDCl₃) δ 2.20-2.40 (m, 2H), 3.00 (t, J=7.5 Hz, 2H), 3.84 (s, 3H), 4.22 (t, J=6.9 Hz, 1H), 6.83 (t, J=55.8 Hz, 1H).

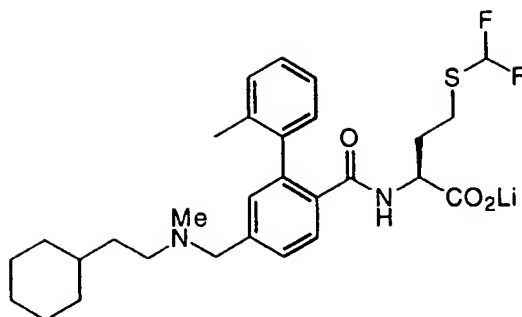
Example 1079E(2S)-2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-difluoromethylthiobutanoate, Methyl Ester

The title compound was prepared according to the procedure in example 608D, replacing L-methionine methyl ester-HCl with S-difluoromethylhomocysteine methyl ester, trifluoroacetate, and was isolated as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 0.80-0.94 (m, 2H), 1.10-1.70 (m, 11H), 1.90-2.18 (m, 5H), 2.20 (s, 3H), 2.30-2.41 (m, 4H), 3.53 (s, 2H), 3.67 (s, 3H), 4.57-5.66 (m, 1H), 5.83-5.90 (m, 1H), 6.73 ("dt", J=2.7, 56 Hz, 1H), 7.14-7.41 (m, 5H), 7.39 (brd, J=7.5 Hz, 1H), 7.90 ("dd", J=14.4, 8.1 Hz, 1H).

MS (ESI(+)) m/e 547 (M+H)⁺.

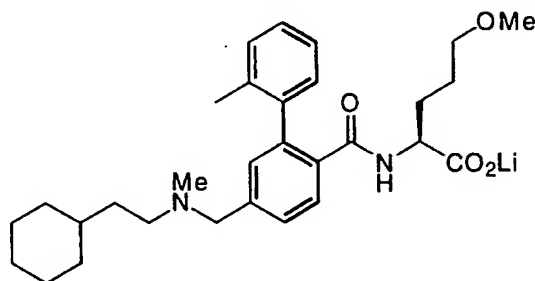
MS (ESI(-)) m/e 545 (M-H)⁻.

Example 1079F

11620 (2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-difluoromethylthiobutanoate, lithium salt

The title compound was prepared from (2S) 2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-difluoromethylthiobutanoate methyl ester according to the procedure described in example 608E with the following
 11625 exceptions: The crude lithium salt was found to be substantially impure by analytical HPLC, and was therefore purified by preparative reverse-phase medium pressure liquid chromatography eluting with a gradient of methanol/water/0.1%TFA. The appropriate fractions were concentrated, dissolved in water (10mL), neutralized (pH=6) with sodium bicarbonate solution, then extracted into chloroform (30mL). The organic extracts were
 11630 washed with brine (20mL), dried (MgSO₄), filtered and concentrated. The free amino acid was dissolved in water, the lithium salt was prepared by addition of one equivalent of 5M LiOH, and the solution was frozen (-78°C) and lyophylized to give the title compound as a light yellow powder.

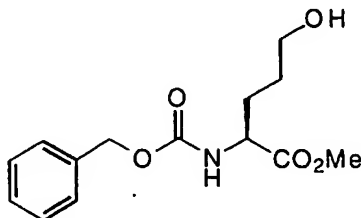
¹H NMR (300 MHz, DMSO) δ 0.75-0.90 (m, 2H), 1.06-1.38 (m, 6H), 1.53-1.80 (m, 9H), 1.94-2.16 (m, 3H), 2.13 (s, 3H), 2.34 (t, J=6 Hz, 2H), 3.49 (s, 2H), 3.60-3.75 (m, 1H), 6.91-7.23 (m, 7H), 7.23 (d, J=7.8 Hz, 1H), 7.50 (d, J=7.8 Hz, 1H).
 11635 MS (ESI(-)) m/e 531 (M-H).



11640

Example 1080

(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-5-methoxypentanoate, lithium salt



11645

Example 1080A

Methyl (2S)-N-2-Carbobenzyloxyamino-5-hydroxypentanoate

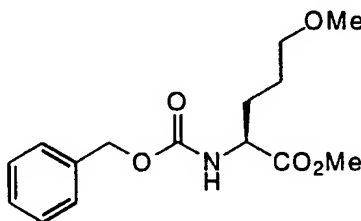
To a solution of N-carbobenzyloxy-L-glutamic acid 1-methyl ester (commercial, 1.0g) in 3.5mL THF at 0°C was added 1M BH₃•THF (6.7mL). After 1h, the reaction was quenched by addition of 1M sodium bisulfate (10mL), and concentrated. The reaction was diluted with water (20mL) and the product was extracted into EtOAc (50mL). The organic extracts were washed with brine (20mL), dried (MgSO₄), filtered and concentrated. The residue was purified by silica gel chromatography eluting with 100% EtOAc to afford a colorless oil (500mg).

11650

11655

MS (ESI(+)) m/e 282 (M+H)⁺, 299 (M+NH₄)⁺.

MS (ESI(-)) m/e 280 (M-H)⁻.



Example 1080B

Methyl (2S)-N-2-Carbobenzyloxyamino-5-methoxypentanoate

11660

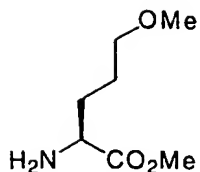
Methyl (2S)-N-2-carbobenzyloxyamino-5-hydroxypentanoate (500mg) was dissolved in ether (10mL), followed by addition of silica gel (2g). Diazomethane solution in ether was added (≈20mL), without observing the persistence of the yellow color of the reagent. The reaction was filtered and concentrated, and the above procedure was repeated. The residue was purified by silica gel chromatography eluting with 50% EtOAc/hexane to afford a colorless oil (236mg, 45%). The yield reflects the poor conversion of the reaction. ¹H NMR (300 MHz, CDCl₃) δ 1.59-2.00 (m, 4H), 3.31 (s, 3H), 3.38 (t, J=6 Hz, 2H), 3.74 (s, 3H), 4.34-4.44 (m, 1H), 5.11 (s, 2H), 5.43 (brd, J=7.8 Hz, 1H), 7.32-7.40 (m, 5H).

11665

11670

MS (ESI(+)) m/e 296 (M+H)⁺, 318 (M+Na)⁺.

MS (ESI(-)) m/e 294 (M-H)⁻.



Example 1080C

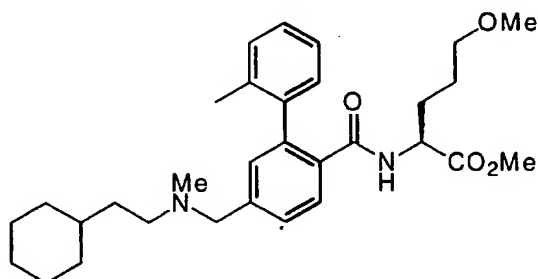
11675

Methyl (2S)-2-amino-5-methoxypentanoate

11680

Methyl (2S)-N-2-carbobenzyloxyamino-5-methoxypentanoate (230mg) was dissolved in methanol (2.5mL) at ambient temperature, followed by addition of ammonium formate (196mg), and 10% palladium on carbon (20mg). The reaction was refluxed for 30min, then cooled, filtered and concentrated. The residue was partitioned between dichloromethane and dilute NaOH. The organic extracts were washed with brine (10mL), dried (MgSO₄), filtered and concentrated to give the title compound (99mg, 78%) as a light yellow syrup.

MS (ESI(+)) m/e 162 (M+H)⁺.



11685

Example 1080D

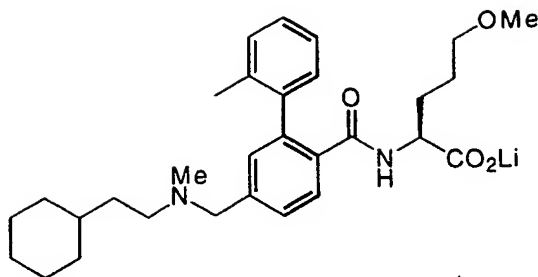
(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-5-methoxypentanoate, Methyl Ester

11690

The title compound was prepared according to example 608D, replacing L-methionine methyl ester·HCl with methyl (2S)-2-amino-5-methoxypentanoate, and was isolated as a colorless oil.

MS (ESI(+)) m/e 509 (M+H)⁺.

MS (ESI(-)) m/e 507 (M-H)⁻.



11695

Example 1080E

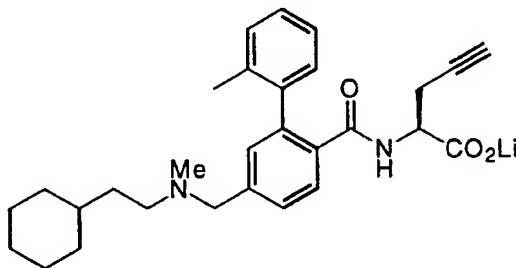
(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-5-methoxypentanoate, lithium salt

11700 (2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-5-methoxypentanoate methyl ester was converted to the title compound according to the procedure in example 608E, and was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 0.74-0.90 (m, 2H), 0.92-1.66 (m, 15H), 1.93-2.14 (m, 3H), 2.13 (s, 3H), 2.34 (t, J=6 Hz, 2H), 3.04-3.12 (m, 2H), 3.17 (s, 3H), 3.49 (s, 2H), 11705 3.58-3.67 (m, 1H), 6.88-6.93 (m, 1H), 7.03-7.23 (m, 5H), 7.30 (d, J=8.1 Hz, 1H), 7.48 (d, J=8.1 Hz, 1H).

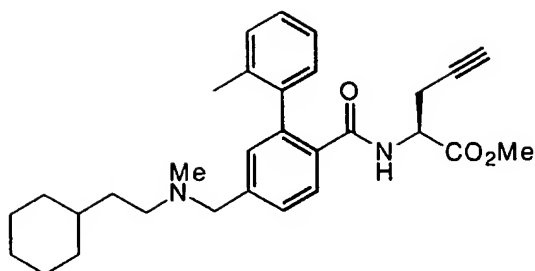
MS (ESI(-)) m/e 493 (M-H); Analysis calc'd for C₃₀H₄₁LiN₂O₄•0.75H₂O: C, 70.09; H, 8.33; N, 5.45; found: C, 70.4; H, 8.20; N, 5.38.

11710

Example 1081

(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]aminopent-4-ynoate, lithium salt

11715

Example 1081A

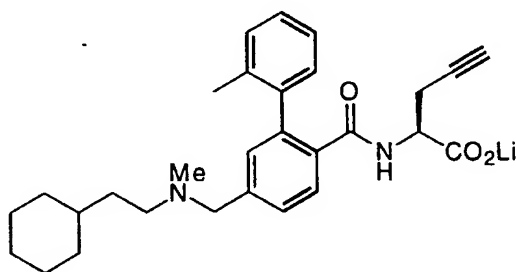
(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]aminopent-4-ynoate, Methyl Ester

11720 The title compound was prepared according to example 608D, replacing L-methionine methyl ester·HCl with L-propargylalanine methyl ester·HCl, and was isolated as a colorless oil.

MS (ESI(+)) m/e 475 (M+H)⁺.

MS (ESI(-)) m/e 473 (M-H)⁻.

11725

Example 1081B

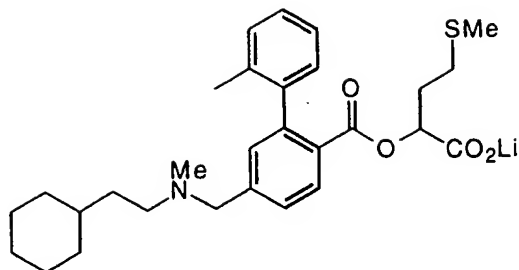
(2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]aminopent-4-ynoate, lithium salt

11730 (2S) 2-N-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]aminopent-4-ynoate methyl ester was converted to the title compound according to the procedure in example 608E, and was isolated as a white powder.

¹H NMR (300 MHz, DMSO) δ 0.74-0.92 (m, 2H), 1.06-1.38 (m, 6H), 1.53-1.66 (m, 5H), 2.04 (s, 3H), 2.10 (m, 1H), 2.14 (s, 3H), 2.32 (t, J=6 Hz, 2H), 2.36-2.43 (m, 2H), 11735 3.49 (s, 2H), 3.56-3.63 (m, 1H), 7.00-7.28 (m, 6H), 7.31 (d, J=7.8 Hz, 1H), 7.52 (d, J=7.8 Hz, 1H).

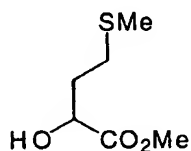
MS (ESI(-)) m/e 459 (M-H); Analysis calc'd for C₂₉H₃₅LiN₂O₃·1.90H₂O: C, 69.56; H, 7.81; N, 5.59; found: C, 69.49; H, 7.33; N, 5.57.

11740

Example 1082

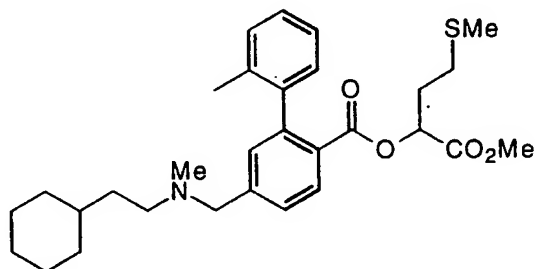
2-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]oxy-4-methylthiobutanoate, lithium salt

11745

Example 1082ADL, 2-Hydroxy-4-methylmercaptobutyric acid, Methyl Ester

A solution of DL, 2-hydroxy-4-methylmercaptobutyric acid calcium salt (2.2g) in 0.5M HCl (50mL) was saturated with sodium chloride, extracted exhaustively with EtOAc, which was dried (MgSO₄), filtered and concentrated. The residue was dissolved in methanol (10mL) and trimethylsilyldiazomethane (2M in hexane) was added until the yellow color persisted for 30min. The reaction was quenched by addition of glacial acetic acid and concentrated. The residue was purified by silica gel chromatography eluting with 30% EtOAc/hexane to give the title compound as a light yellow oil (1.37g).

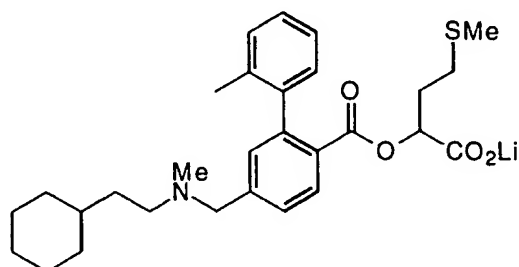
¹H NMR (300 MHz, CDCl₃) δ 1.86-1.98 (m, 1H), 2.04-2.16 (m, 1H), 2.11 (s, 3H), 2.63 (d, J=7.8 Hz, 1H), 2.65 (dd, J=7.8, 1.5 Hz, 1H), 2.88 (brs, 1H), 3.81 (s, 3H), 3.34 (dd, J=7.8, 3.9 Hz, 1H).

Example 1082B

2-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]oxy-4-methylthiobutanoate, Methyl Ester

11760

To a solution of DL, 2-hydroxy-4-methylmercaptobutyric acid methyl ester (72mg) and N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid (example 608C, 150mg) in THF (1.0mL) was added triphenylphosphine (127mg) and diethyl azodicarboxylate (0.075mL). After 6h, the reaction was concentrated, and the residue was purified by silica gel chromatography eluting with 20% EtOAc/hexane to give the title compound as a colorless oil (90mg, 43%). MS(APCI(+)) 512 (M+H)⁺.



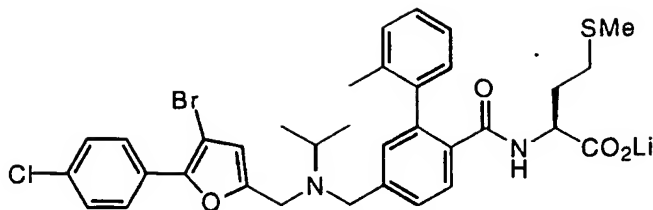
Example 1082C

2-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]oxy-4-methylthiobutanoate, lithium salt

2-[4-(N-2-Cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]oxy-4-methylthiobutanoate methyl ester (180mg) was dissolved in methanol (1.2mL) and 5M LiOH (0.088mL) was added, followed by addition of THF (0.5mL) to homogenize the reaction. After 4h, additional 5M LiOH (0.088mL) was added. After 1.5h, the reaction was concentrated, and the residue was dissolved in water (40mL). The aqueous solution was washed once with ether (20mL), then acidified, and the product was extracted into chloroform (3X20mL). The organic extracts were washed with brine (20mL), dried (MgSO₄), filtered and concentrated to give an oily foam (123mg). This residue was dissolved in 1:1 acetonitrile/water (30mL), and 5M LiOH (0.05mL) was added. The solution was frozen (-78°C) and lyophilized to afford the title compound as a very hygroscopic white powder (104mg).

¹H NMR (300 MHz, DMSO) δ 0.76-0.89 (m, 2H), 1.06-1.37 (m, 6H), 1.53-1.68 (m, 7H), 1.93-2.10 (m, 7H), 2.13 (s, 3H), 2.32 (t, J=7.2 Hz, 2H), 3.52 (s, 2H), 4.56-4.66 (m, 1H), 6.93-7.02 (m, 1H), 7.02-7.24 (m, 5H), 7.36-7.41 (m, 1H), 7.82 (d, J=7.8 Hz, 0.3H), 7.87 (d, J=7.8 Hz, 0.7H).

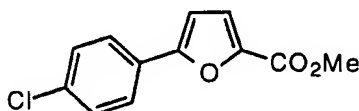
MS (APCI(-)) m/e 496 (M-H); Analysis calc'd for C₂₉H₃₈NO₄SLi•1.65H₂O: C, 65.31; H, 7.80; N, 2.63; found: C, 65.36; H, 7.76; N, 2.57.



11795

Example 1085

N-[4-(N-(5-bromo-(4-chlorophenyl)furan-2-yl)methyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

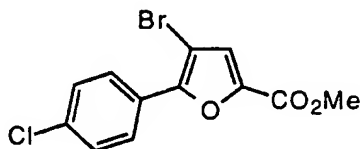


11800

Example 1085A

5-(4-chlorophenyl)-2-furoic acid, methyl ester

To a solution of 5-(4-chlorophenyl)-2-furoic acid (5.0 g, 22 mmol) in MeOH (50 mL) was added conc. H₂SO₄ (4 drops) and the resulting solution heated to 50 °C for 4 days. The reaction was cooled and concentrated in vacuo. The residue was taken up in EtOAc (100 mL) and washed with saturated aqueous NaHCO₃ (2 x 20 mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 19:1) to give 3.8 g (72%) of a cream powder; MS m/z 254 (M⁺ + 18, 100).

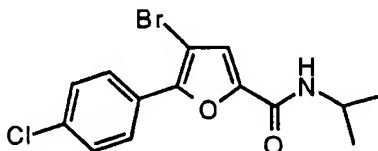


11810

Example 1085B

5-(4-chlorophenyl)-4-bromo-2-furoic acid, methyl ester

To a stirred solution of the ester (3.53 g, 14.9 mmol) in CHCl₃ (40 mL) was added a 4.2 M solution of Br₂ in CHCl₃ (4.3 mL, 17.9 mmol) and the resulting solution heated to 50 °C overnight. The reaction was concentrated in vacuo and the residue was purified by flash chromatography (hexane EtOAc 19:1) to give 3.0 g (64%) of a white powder; MS m/z 334 (M⁺ + 18, 100).



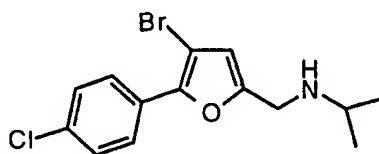
11820

Example 1085C

The ester (1.37 g, 4.34 mmol) was hydrolyzed as in example 1084 D (for 1 hour at rt) and coupled to isopropylamine as in example 1084 D to give 1.31 g (88 %) of a beige powder;

MS m/z 361 ($M^+ + 18$, 100).

11825

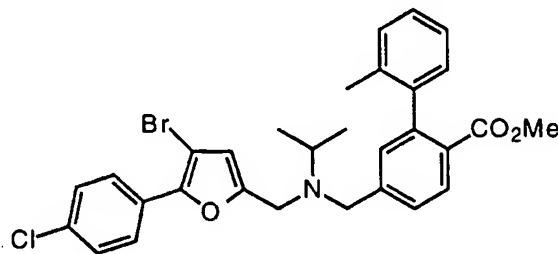
Example 1085C

11830

To a stirred solution of the amide (1.12 g, 3.27 mmol) in dichloroethane (50 mL) was added tetrabutylammonium borohydride (2.5 g, 9.8 mmol) and the resulting solution heated to 50 °C overnight. The reaction was concentrated in vacuo and the residue taken up in EtOAc (50 mL) and quenched with water (20 mL). The layers were separated and the organic layer washed with H₂O (20 mL) and brine (20 mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc 2:1) to give 0.49 g (46%) of a light yellow oil;

11835

MS m/z 330 ($M^+ + 1$, 100).

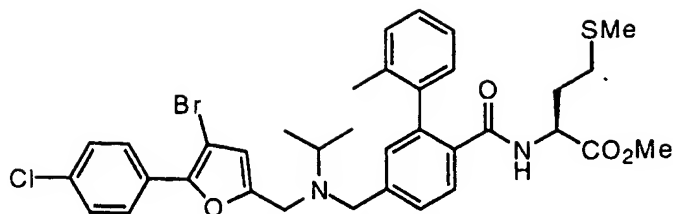
Example 1085D

11840

To a stirred solution of the amine (0.485 g, 1.48 mmol) in acetonitrile (10 mL) was added the core benzyl bromide (see example 1178D) (0.472 g, 1.48 mmol), tetrabutylammonium iodide (0.055 g, 0.15 mmol), and K₂CO₃ (0.41 g, 3.0 mmol) and the resulting solution heated to 70 °C overnight. The reaction was cooled and concentrated in vacuo. The residue was taken up in EtOAc (30 mL) and washed with H₂O (10 mL), saturated aqueous NaHCO₃ (10 mL), brine (10 mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 19:1) to give 0.63 g (75%) of a light yellow oil;

11845

MS m/z 568 ($M^+ + 1$, 100).

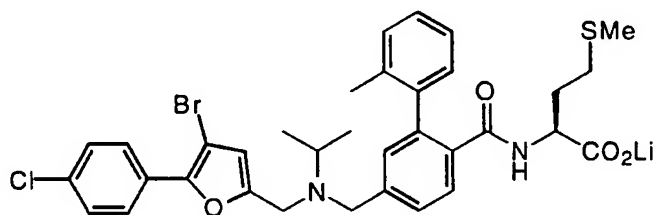


11850

Example 1085E

N-[4-(N-(5-bromo-(4-chlorophenyl)furan-2-yl)methyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

The ester (0.61 g, 1.1 mmol) was hydrolyzed as in example 1084 D and coupled to
 11855 L-methionine methyl ester hydrochloride as in example 1084 D. Flash chromatography
 (hexane/EtOAc 4:1) gave 0.57 g (77 %) of an orange oil;
 MS m/z 697 ($M^+ + 1$, 100).



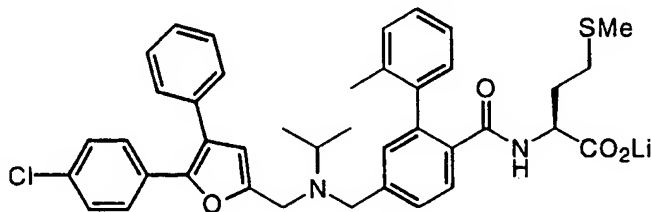
11860

Example 1085F

N-[4-(N-(5-bromo-(4-chlorophenyl)furan-2-yl)methyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

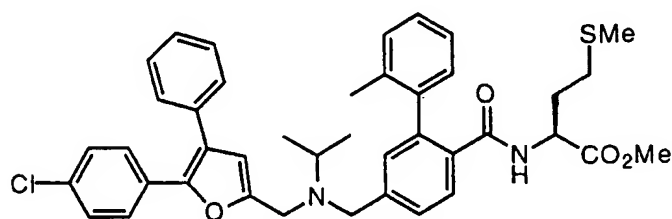
The ester (54 mg, 0.077 mmol) was hydrolyzed as in example 1084 E to give 53 mg
 of a beige powder;
 11865 ^1H NMR (DMSO- d_6) δ 7.72-7.67 (m, 2 H), 7.45-7.29 (m, 4 H), 7.11-6.82 (m, 6 H), 6.51
 (s, 1 H), 3.63-3.48 (m, 5 H), 2.92-2.88 (m, 1 H), 2.04-1.73 (m, 8 H), 1.65-1.59 (m, 1
 H), 1.53-1.47 (m, 1 H), 1.01-0.97 (m, 6 H);
 MS m/z 683 ($M^+ - 1$, 100).

11870

Example 1086

N-[4-(N-(5-phenyl)-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

11875

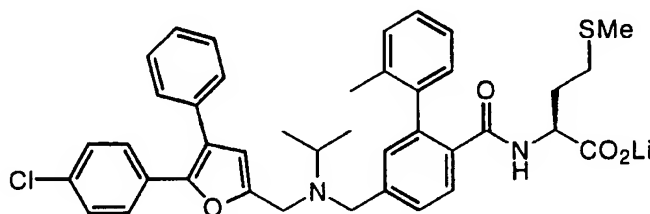


Example 1086A

N-[4-(N-(5-phenyl)-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

11880 To a solution of the bromo ester (60 mg, 0.086 mmol) in DME (5 mL) was added benzenboronic acid (21 mg, 0.17 mmol), CsF (39 mg, 0.26 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (7 mg, 0.009 mmol) and the resulting mixture heated to 80 °C overnight. The reaction was cooled and the reaction filtered through Celite, washing the bed with EtOAc. The filtrate was

11885 concentrated in vacuo and the residue purified by flash chromatography (hexane EtOAc 4:1) to give 31 mg (52%) of a yellow oil; MS m/z 695 (M⁺ + 1, 100).



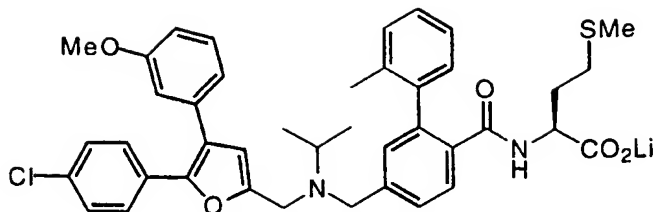
Example 1086B

N-[4-(N-(5-phenyl)-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

The ester (30 mg, 0.04 mmol) was hydrolyzed as in example 1084 E to give 30 mg of a cream powder;

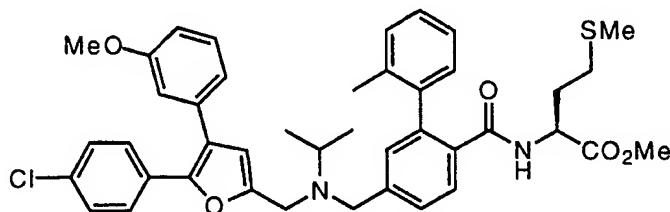
11895 ¹H NMR (DMSO-d₆) δ 7.47-6.85 (m, 17 H), 6.47 (s, 1 H), 3.73-3.58 (m, 5 H), 3.06-3.01 (m, 1 H), 2.11-1.77 (m, 8 H), 1.63-1.57 (m, 1 H), 1.51-1.43 (m, 1 H), 1.05-1.01 (m, 6 H); MS m/z 679 (M⁺ - 1, 100).

11900

Example 1087

N-[4-(N-(5-(3-methoxyphenyl)-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

11905

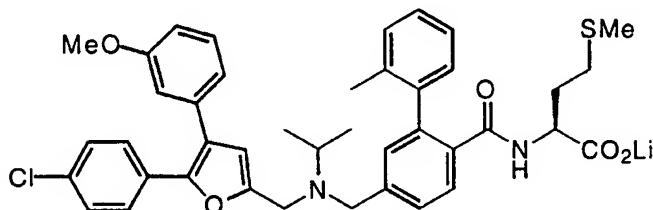
Example 1087A

N-[4-(N-(5-(3-methoxyphenyl)-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

11910

The bromo ester (62 mg, 0.088 mmol) was coupled to m-methoxybenzeneboronic acid as in example 1086 A. Flash chromatography (hexane/EtOAc 4:1) gave 38 mg (55%) of an oil;

MS m/z 725 ($M^+ + 1$, 100).



11915

Example 1087B

N-[4-(N-(5-(3-methoxyphenyl)-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

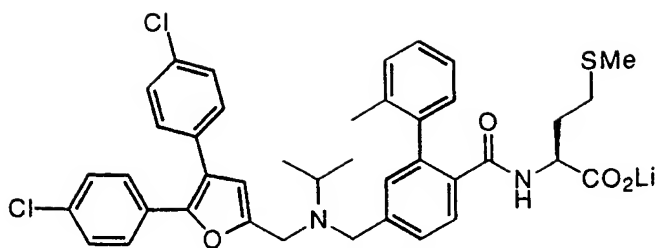
The ester (38 mg, 0.054 mmol) was hydrolyzed as in example 1084 E to give 38 mg of a beige powder;

11920

^1H NMR (DMSO- d_6) δ 7.69-7.02 (m, 12 H), 6.84-6.79 (m, 4 H), 6.42 (s, 1 H), 3.65-3.48 (m, 8 H), 2.97-2.93 (m, 1 H), 2.04-1.75 (m, 8 H), 1.63-1.57 (m, 1 H), 1.51-1.43 (m, 1 H), 1.03-0.98 (m, 6 H);

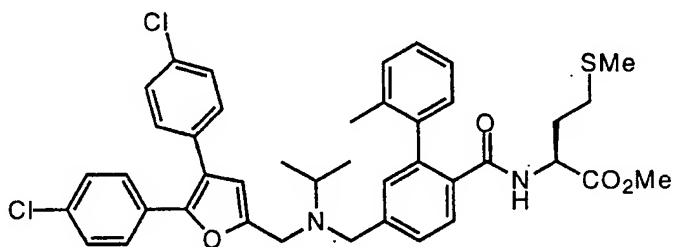
MS m/z 709 ($M^+ - 1$, 100).

11925

**Example 1088**

N-[4-(N-(4,5-di(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

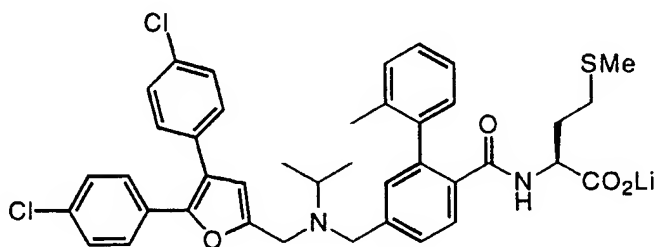
11930

**Example 1088A**

N-[4-(N-(4,5-di(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-
methylphenyl)benzoyl]methionine, methyl ester

11935

The bromo ester (80 mg, 0.11 mmol) was coupled to p-chlorobenzeneboronic acid as in example 1086 A. Flash chromatography (hexane/EtOAc 4:1) gave 38 mg (46 %) of an oil; MS m/z 729 ($M^+ + 1$, 100).

**Example 1088B**

N-[4-(N-(4,5-di(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-
methylphenyl)benzoyl]methionine, lithium salt

11940

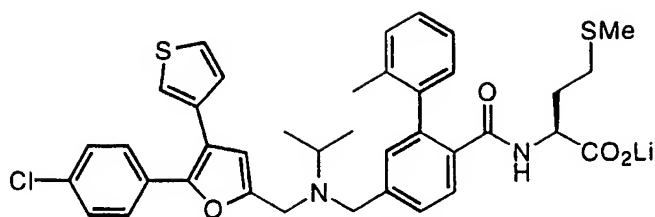
The ester (31 mg, 0.042 mmol) was hydrolyzed as in example 1084 E to give 31 mg
 of a cream powder;

11945

^1H NMR (DMSO- d_6) δ 7.47-7.29 (m, 11 H), 7.22-7.03 (m, 4 H), 6.89-6.87 (m, 1 H)
 6.48 (s, 1 H), 3.73-3.62 (m, 5 H), 3.03-2.97 (m, 1 H), 2.08-1.83 (m, 8 H), 1.68-1.63 (m,
 1 H), 1.57-1.51 (m, 1 H), 1.11-1.05 (m, 6 H);

MS m/z 713 ($M^+ - 1$, 100).

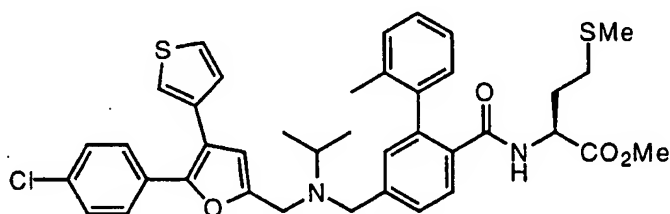
11950



Example 1089

N-[4-(N-(5-thien-3-yl-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

11955

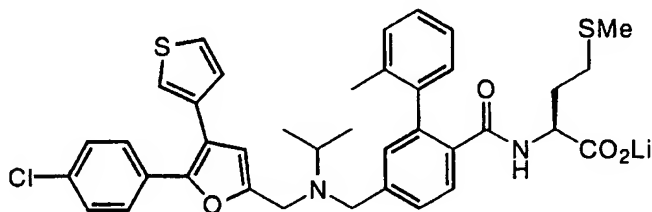


Example 1089A

N-[4-(N-(5-thien-3-yl-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

11960

The bromo ester (56 mg, 0.084 mmol) was coupled to 2-thiopheneboronic acid as in example 1086 A. Flash chromatography (hexane/EtOAc 4:1) gave 41 mg (73 %) of an oil; MS m/z 701 ($M^+ + 1$, 100).



Example 1089B

N-[4-(N-(5-thien-3-yl-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt

11965

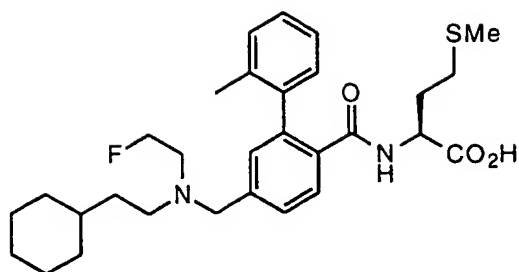
The ester (38 mg, 0.054 mmol) was hydrolyzed as in example 1084 E to give 37 mg of a yellow powder;

11970

^1H NMR (DMSO- d_6) δ 7.46-7.32 (m, 7 H), 7.11-6.99 (m, 7 H), 6.84-6.82 (m, 1 H), 6.43 (s, 1 H), 3.65-3.60 (m, 5 H), 2.96-2.92 (m, 1 H), 2.03-1.75 (m, 8 H), 1.63-1.58 (m, 1 H), 1.52-1.47 (m, 1 H), 1.02-0.99 (m, 6 H);

MS m/z 385 ($M^+ - 1$, 100).

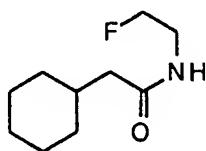
11975



Example 1094

N-[4-(N-(2-cyclohexylethyl)-N-2-fluoroethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

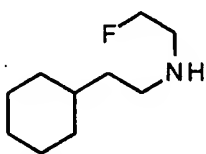
11980



Example 1094A

N-(2-Fluoroethyl)-2-cyclohexylacetamide

11985 Following the procedure of example 1178E, 2-fluoroethylamine•HCl (1.00 g, 10.00 mmol) provided 1.58 g (84%) of the title compound.
MS (DCI, NH_3): 188 (MH^+).



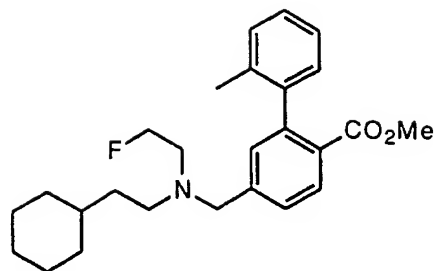
11990

Example 1094B

N-(2-Fluoroethyl)-N-2-cyclohexylethylamine

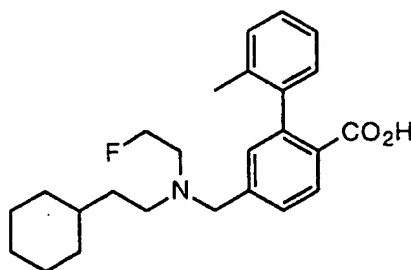
Following the procedure of example 1178F, example 1094A (1.54 g, 8.2 mmol) provided 1.30 g (92%) of the title compound.
MS (DCI, NH_3): 172 (MH^+).

11995

Example 1094C

N-[4-(N-(2-cyclohexylethyl)-N-2-fluoroethylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester

12000 Following the procedure of example 1178G and substituting potassium phosphate for diisopropylethylamine, and heating at 60°C for 60 hours, example 1094B (188 mg, 1.10 mmol) provided 288 mg (70%) of the title compound.
MS (ESI +): 410 (M + NH₄⁺ - F⁻).



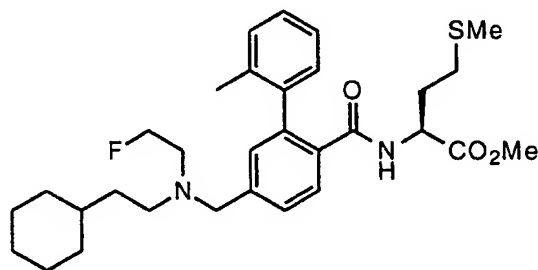
12005

Example 1094D

N-[4-(N-(2-cyclohexylethyl)-N-2-fluoroethylaminomethyl)-2-(2-methylphenyl)benzoic acid

Following the procedure of example 1178H, example 1094C (0.28 g, 0.68 mmol) provided 0.25 g (93%) of the title compound.

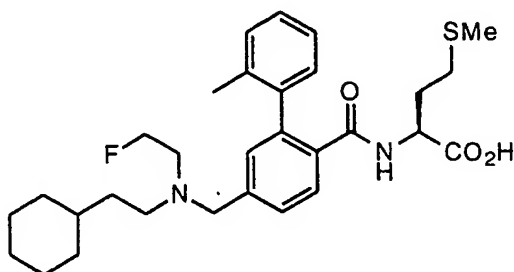
12010 MS (DCI, NH₃): 398 (MH⁺).

Example 1094E

N-[4-(N-(2-cyclohexylethyl)-N-2-fluoroethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

12015

Following the procedure of example 1178 I, example 1094D (245 mg, 0.62 mmol) provided 257 mg (77%) of the title compound. MS: (ESI+): 541 (MH)⁺; (ESI-); 539 (M-H).



12020

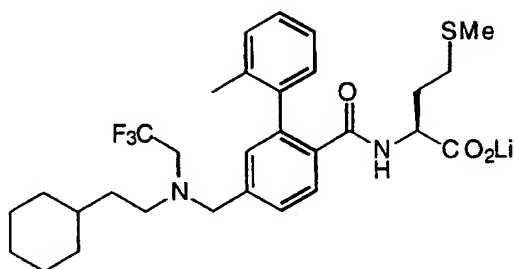
Example 1094F

N-[4-(N-(2-cyclohexylethyl)-N-2-fluoroethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104D, example 1094E (250 mg, 0.46 mmol) provided 240 mg of the title compound.

12025

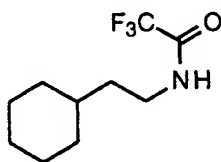
¹H NMR (δ, CDCl₃): 7.75 (2H), 7.0-7.4 (4H), 6.4 (1H), 3.8-4.6 (9H), 2.9-3.3 (4H), 0.8-2.3 (21H). MS: (ESI+): 527 (MH)⁺; (ESI-); 525 (M-H). Calc'd for C₃₀H₄₁FN₂O₃S•0.90H₂O: C 66.12 H 7.92 N 5.14; Found: C 66.13 H 7.77 N 4.86.



12030

Example 1103

N-[4-(N-(2-cyclohexylethyl)-N-2,2,2-trifluoroethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt



12035

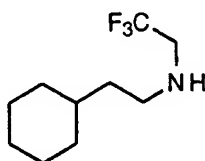
Example 1103A

N-trifluoroacetyl-2-cyclohexylethyl amide

Cyclohexylethylamine (1.27 g, 10 mmol) was dissolved in 10 mL of methylene chloride and pyridine (1.8 mL, 15.0 mol) was added and the mixture cooled to -10° C in an

12040 ice/acetone bath. The solution was treated with trifluoroacetic anhydride (1.7 mL, 12.0 mmol) in 5 mL of methylene chloride dropwise. After stirring for 2 hours at 0°C the mixture was diluted with 100 mL of ether and extracted with water, 1M aqueous phosphoric acid and saturated aqueous sodium bicarbonate, dried, filtered and concentrated to give a white solid (2.07g, 92%).

12045 MS (DCI, NH₃): 241 (M+NH₄)⁺.



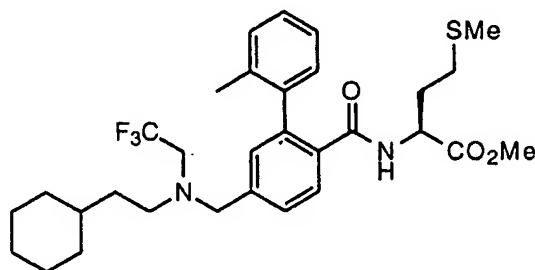
Example 1103B

N-2-trifluoroethyl-2-cyclohexylethyl amine

12050 A solution of lithium aluminum hydride (9 mL of a 1M solution in THF, 9 mmol) was added to a solution of example 1103A (0.67 g, 3.0 mmol) and the mixture was heated to reflux for 2 hours and then cooled to room temperature. The reaction was quenched by the same procedure as example 1178F to provide 0.58 g (92%) of the title compound.

MS (DCI, NH₃): 228 (M+NH₄)⁺.

12055



Example 1103C

N-[4-(N-(2-cyclohexylethyl)-N-2,2,2-trifluoroethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

12060 A solution of example 1103B (210 mg, 1.0 mmol) and the aldehyde from example 403G (192 mg, 0.5 mmol) in 3 mL of 1,2 dichloroethane was treated with acetic acid (0.14 mL, 2.5 mmol) and the mixture stirred for 10 minutes. The mixture was treated with sodium triacetoxyborohydride (213 mg, 1.0 mmol) and the mixture stirred overnight. The work-up was the same as that of example 1134E. The crude product was purified by chromatography on silica gel (20 g, 20% ethyl acetate/hexanes) to provide 96 mg (33%) of the title compound.

12065

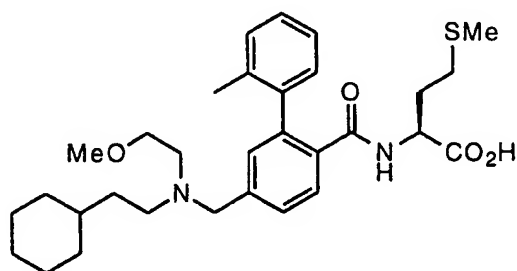
¹H NMR (300 MHz., CDCl₃): δ 7.91, dd, 1H; 7.42, dd, 1H; 7.18 - 7.36, m, 4H; 7.15, bs, 1H; 5.88, bd, 1H; 4.63, m, 1H; 3.83, s, 2H; 3.65, s, 3H; 3.09, q, 2H; 2.64, t, 2H; 2.18,

s, 1.5 H (o-tolyl); 2.07, s, 1.5H (o-tolyl); 2.05, m, 1H; 2.03, s, 1.5H (MeS); 2.01, s, 1.5H (MeS); 1.87, m, 1H; 1.61, bm, 6H; 1.35, m, 2H; 1.20, m 2H; 1.14, m, 2H; 0.85, m, 2H.
MS (ESI+): 579 (MH+); (ESI-): 577 (M-H).

Prepared according to the procedure of example 1178J.

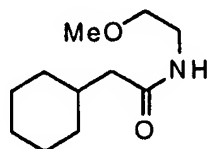
¹H NMR (300 MHz., dmso d6): δ 7.52, d, 1H; 7.35, d, 1H; 7.23, m, 3H; 7.12, m, 3H; 6.91, d, 1H; 3.81, s, 2H; 3.66, m, 1H; 3.38, q, 2H; 2.56, t, 2H; 2.06, m, 1H; 2.00, bs, 3H; 1.92, s, 3H; 1.58, m, 7H; 1.00 - 1.38, m, 6H; 0.80, m, 2H.

MS (ESI+): 587; 571; 565 (MH+); (ESI-): 563 (M-H). Calc'd for C₃₀H₃₈LiN₂O₃S•1.75 H₂O; C 59.84; H 6.95; N 4.65; Found: C 59.86; H 6.57; N 4.45.



Example 1104

N-[4-(N-(2-cyclohexylethyl)-N-2-methoxyethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine



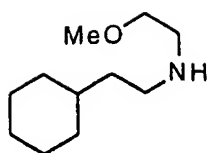
Example 1104A

N-(2-methoxyethyl)-2-cyclohexylacetamide

The acid chloride from example 1178E (1.60 g, 10 mmol) in 10 mL of methylene chloride was added dropwise to a cold (0°C) solution of 2-methoxyethylamine (1.3 mL, 15 mmol) and pyridine (1.9 mL, 22 mmol) in 10 mL of methylene chloride and the mixture was stirred overnight. The mixture was diluted with ethyl ether and washed with water, 1M aqueous phosphoric acid, 2M aqueous sodium carbonate and brine, dried, filtered and concentrated to provide 1.70 g (85%) of the title compound as a white solid.

¹H NMR (300 MHz., CDCl₃): δ 5.89, bs, 1H; 3.46, m, 4H; 3.37, s, 3H; 2.05, d, 2H; 1.79, m, 1H; 1.70, bm, 6H; 1.24, m, 2H; 1.17, m, 1H; 0.95, m, 2H.

MS (DCI, NH₃): 200 (MH+).



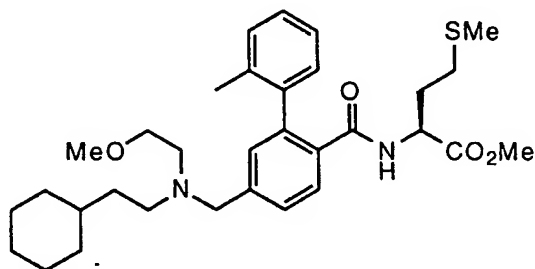
12100

Example 1104BN-(2-methoxyethyl)-N-2-cyclohexylethylamine

Using the procedure of example 1178F, example 1104A (1.70 g, 8.54 mmol) provided the title compound (1.56 g, 100%).

MS (DCI, NH₃): 186 (MH⁺).

12105

Example 1104C

N-[4-(N-(2-cyclohexylethyl)-N-2-methoxyethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

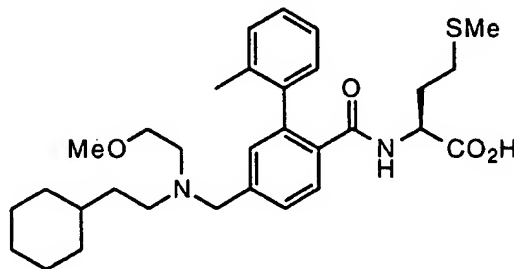
12110

Using the procedure of example 1103C, example 1104B (186 mg, 1.0 mmol) and example 403G (192 mg, 0.5 mmol) were combined to provide 78 mg (28%) of the title compound.

¹H NMR (300 MHz., CDCl₃): δ 7.91, dd, 1H; 7.42, dd, 1H; 7.18 - 7.37, m, 4H; 7.17, bs, 1H; 5.89, bd, 1H; 4.64, m, 1H; 3.68, s, 2H; 3.66, s, 3H; 3.45, t, 2H; 3.31, s, 3H; 2.66, t, 2H; 2.50, t, 2H; 2.19, s, 1.5H (o-tolyl); 2.07, s, 1.5H (o-tolyl); 2.05, m, 1H; 2.03, s, 1.5H (SMe); 2.01, s, 1.5H (SMe); 1.85, m, 1H; 1.63, bm, 6H; 1.34, m, 2H; 1.06 - 1.29, m, 4H; 0.88, m, 2H.

12115

MS (ESI⁺): 555 (MH⁺); (ESI⁻): 553 (M-H).



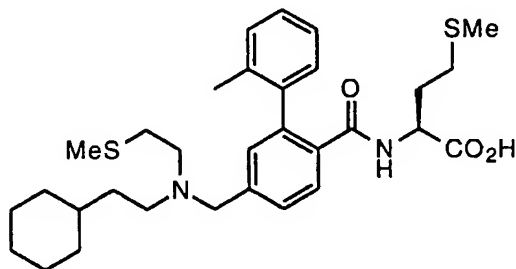
12120

Example 1104D

N-[4-(N-(2-cyclohexylethyl)-N-2-methoxyethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

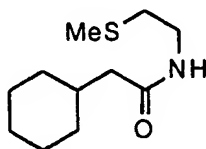
12125 A solution of example 1104C (73 mg, 0.13 mmol) in 2 mL of 3:1 THF/methanol was cooled in an ice bath and treated with lithium hydroxide (0.26 mL of a 1M aqueous solution, 0.26 mmol) and the mixture stirred overnight and then concentrated. The solid was diluted with water and the pH adjusted to 4.5 with 1M aqueous phosphoric acid and then extracted with 3 portions of ethyl acetate. The combined organic fractions were washed with brine, dried filtered and concentrated. The residue was lyophilized to provide 70 mg of the title compound.

12130 ¹H NMR (300 MHz., CD₃OD): δ 7.74, d, 1H; 7.58, d, 1H; 7.37, m, 1H; 7.10 - 7.31, m, 4H; 4.50, m, 3H; 3.66, t, 2H; 3.37, s, 3H; 3.22, t, 2H; 3.04, m, 2H; 2.22, bs, 1H; 2.10, m, 3H; 1.97, s, 3H; 1.90, m, 2H; 1.53 - 1.77, m, 8H; 1.14 - 1.38, m, 4H; 0.96, m, 2H. MS (ESI+): 541 (MH⁺); (ESI-): 539 (M-H). Calc'd for C₃₁H₄₄N₂O₄S•0.85 H₂O; C 66.96; 12135 H 8.28; N 5.04; Found: C 66.97; H 8.34; N 4.87.



Example 1105

12140 N-[4-(N-(2-cyclohexylethyl)-N-2-methylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

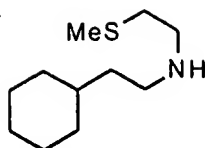


Example 1105A

12145 N-(2-methylthioethyl)-2-cyclohexylacetamide

Following the procedure of example 1104A, 2-methylthioethylamine (1.0 g, 11 mmol) was converted to the title compound (1.77 g, 89%).

MS (DCI, NH₃): 216 (MH⁺); 233 (M+NH₄)⁺.



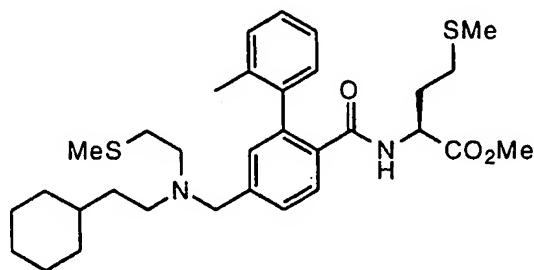
12150

Example 1105BN-(2-methylthioethyl)-2-cyclohexylethylamine

Using the procedure of example 1178F, example 1105A (1.75 g, 8.44 mmol) was converted into the title compound (1.63 g, 100%).

12155

MS (DCI, NH₃): 202 (MH⁺).

Example 1105C

N-[4-(N-(2-cyclohexylethyl)-N-2-methylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

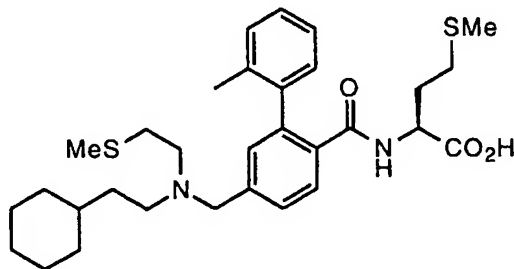
12160

Using the procedure of example 1103C, example 1105B (201 mg, 1.0 mmol) and example 403G (192 mg, 0.5 mmol) were combined to provide 151 mg (53%) of the title compound.

¹H NMR (300 MHz, CDCl₃): δ 7.91, dd, 1H; 7.42, dd, 1H; 7.18 - 7.37, m, 4H; 7.17, bs, 1H; 5.89, bd, 1H; 4.63, m, 1H; 3.66, s, 3H; 3.63, s, 2H; 2.68, m, 2H; 2.59, m, 2H; 2.48, t, 2H; 1.99 - 2.21, m, 10H; 1.85, m, 1H; 1.62, bm, 6H; 1.36, m, 2H; 1.06 - 1.30, m, 4H; 0.87, m, 2H.

12165

MS (ESI⁺): 571 (MH⁺); (ESI⁻): 569 (M-H).



12170

Example 1105D

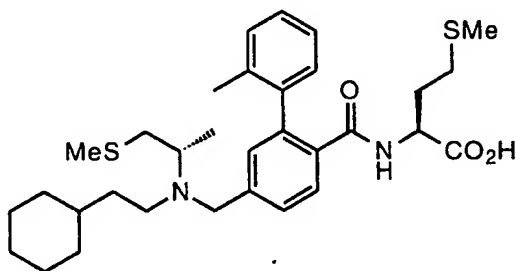
N-[4-(N-(2-cyclohexylethyl)-N-2-methylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

A solution of example 1105C (145 mg, 0.25 mmol) in 2 mL of 3:1 THF/methanol was cooled in an ice bath and treated with lithium hydroxide (0.5 mL of a 1M aqueous solution, 0.5 mmol) and the mixture stirred overnight. The solution was concentrated to dryness and diluted with water and the pH adjusted to 4.5 with 1M aqueous phosphoric acid. The solid collected was by filtration and dried in the air to provide 130 mg (93%) of the title compound.

¹H NMR (300 MHz., CD₃OD): δ 7.71, d, 1H; 7.57, d, 1H; 7.35, d, 1H; 7.10 - 7.31, m, 4H; 4.32, m, 1H; 4.17, s, 2H; 3.10, m, 2H; 2.94, m, 2H; 2.76, m, 2H; 2.22, bs, 1H; 2.02 - 2.09, m, 3H; 2.10, s, 3H; 1.99, s, 3H; 1.89, m, 2H; 1.68, m, 6H; 1.56, m, 2H; 1.09 - 1.26, m, 4H; 0.93, m, 2H.

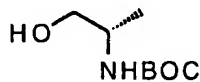
MS (ESI+): 557 (MH+); (ESI-): 555 (M-H). Calc'd for C₃₁H₄₄N₂O₃S₂•0.50 H₂O; C

65.80; H 8.02; N 4.95; Found: C 65.79; H 7.89; N 4.79.



Example 1106

N-[4-(N-(2-cyclohexylethyl)-N-1-methyl-2(S)-methylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine



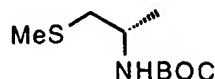
Example 1106A

2(S)-N-t-butoxycarbonylaminopropan-1-ol

A stirred solution of 2(S)-amino-1-propanol (1.0 g, 13.3 mmol) in 20 mL of methylene chloride was treated with di-tertbutyldicarbonate (3.19 g, 14.6 mmol) in 5 mL of methylene chloride and then the solution was treated with 10 mL of 2M aqueous sodium carbonate and stirred for 2 hours. The biphasic mixture was diluted with water and the layers were separated. The aqueous layer was extracted with methylene chloride and the combined organic layers were dried, filtered and concentrated to provide 2.35 g (105%) of the title compound.

¹H NMR (300 MHz., CDCl₃): δ 4.59, bs, 1H; 3.77, m, 1H; 3.64, dd, 1H; 3.52, dd, 1H; 2.42, bs, 1H; 1.44, s, 9H; 1.14, d, 3H.

12205 MS (DCI, NH₃): 176 (MH)⁺; 193 (M+NH₄)⁺.



Example 1106B

1-Methylthio-2(S)-N-t-butoxycarbonylaminopropane

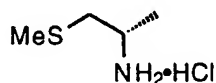
12210 A stirred solution of example 1106A (350 mg, 2.0 mmol) in 6 mL of methylene chloride was cooled in an ice/acetone bath and sequentially treated with triethylamine (0.34 mL, 2.4 mmol) and methanesulfonyl chloride (0.17 mL, 2.2 mmol) and the mixture stirred for 2 hours and then diluted with ether, extracted with water, 1M aqueous phosphoric acid, brine, dried filtered and concentrated to provide a yellow oil that was used directly. The

12215 mesylate was dissolved in 2 mL of DMF and added to a mixture of sodium thiomethoxide (280 mg, 4.0 mmol) and 5 mL of DMF and the mixture was stirred for 2 hours. The reaction was quenched by the addition of water and the mixture diluted with water and ethyl acetate. The layers were separated and the mixture was extracted with 2 additional portions of ethyl acetate and the combined organic layers washed with water and brine, dried, filtered and

12220 concentrated to provide 328 mg (80% overall) of the title compound.

¹H NMR (300 MHz., CDCl₃): δ 3.86, bs, 1H; 2.65, dd, 1H; 2.56, dd, 1H; 2.14, s, 3H; 1.45, s, 9H; 1.22, d, 3H.

MS (DCI, NH₃): 206 (MH)⁺; 223 (M+NH₄)⁺.



12225

Example 1106C

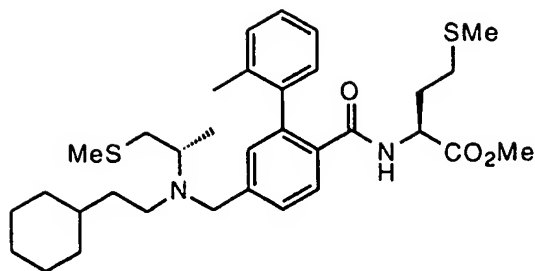
1-Methylthio-2(S)-aminopropane hydrochloride salt

Example 1106B (320 mg, 1.56 mmol) was dissolved in 2 mL of 4N HCl/dioxane and stirred for 1 Hour. The mixture was diluted with ether and filtered to provide 103 mg

12230 (53%) of the title compound as a white solid.

¹H NMR (300 MHz., CDCl₃): δ 8.56, bs, 3H; 3.51, m, 1H; 2.89, dd, 1H; 2.78, dd, 1H; 2.17, s, 3H; 1.54, d, 3H.

MS (DCI, NH₃): 123 (M+NH₄)⁺.



12235

Example 1106DN-[4-(N-(2-cyclohexylethyl)-N-1-methyl-2(S)-methylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

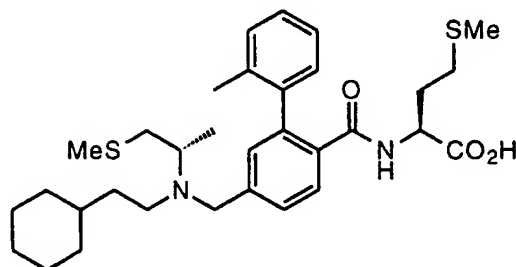
12240 Part 1. Following the general procedure of example 403H, example 1106C (98 mg, 0.69 mmol), example 403G (243 mg, 0.63 mmol), diisopropylethylamine (0.12 mL, 0.69 mmol) and acetic acid (0.18 mL, 3.14 mmol) were stirred in 4 mL of 1,2-dichloroethane for 2 hours and then treated with sodium triacetoxyborohydride (263 mg, 1.26 mmol). This procedure yielded 332 mg of material that was used in the next step.

12245 Part 2. The amine prepared in part 1 was treated with 2-cyclohexylacetaldehyde (159 mg, 1.26 mmol), acetic acid (0.36 mL, 6.3 mmol) and stirred for 2 hours. This solution was treated with sodium triacetoxyborohydride (263 mg, 1.26 mmol) and the mixture stirred overnight. The mixture was quenched and worked-up as described in example 403H. The residue obtained was purified by column chromatography on silica gel (20 g, 20% ethyl acetate/hexanes) to provide 225 mg (61% overall) of the title compound.

12250 ¹H NMR (300 MHz., CDCl₃): δ 7.89, dd, 1H; 7.47, d, 1H; 7.15 - 7.37, m, 5H; 5.87, bd, 1H; 4.63, m, 1H; 3.67, d, 1H; 3.65, s, 3H; 3.55, d, 1H; 2.96, m, 1H; 2.75, dd, 1H; 2.44, m, 2H; 2.37, dd, 1H; 1.99 - 2.22, m, 10H; 1.84, m, 1H; 1.60, m, 6H; 1.09 - 1.33, m, 6H; 1.08, d, 3H; 0.72 - 1.00, m, 2H.

MS (ESI⁺): 585 (MH⁺); (ESI⁻): 583 (M-H).

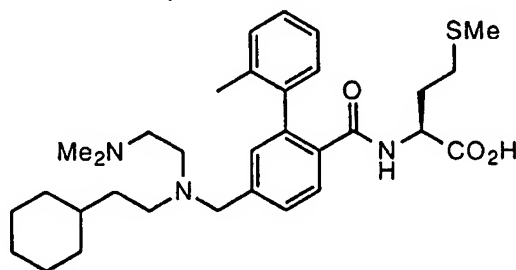
12255

Example 1106N-[4-(N-(2-cyclohexylethyl)-N-1-methyl-2(S)-methylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

12260 Following the procedure of example 1105D, example 1106D (210 mg, 0.36 mmol) provided 110 mg (53%) of the title compound.

¹H NMR (300 MHz., CD₃OD): δ 7.69, d, 1H; 7.56, bd, 1H; 7.37, bd, 1H; 7.09 - 7.32, m, 4H; 4.33, m, 1H; 4.16, m, 1H; 4.00, m, 1H; 3.32, dt, 1H; 2.89, m, 3H; 2.64, m, 1H; 2.23, bs, 1H; 2.06, m, 2H; 2.04, s, 3H; 1.98, s, 3H; 1.89, m, 2H; 1.65, m, 6H; 1.44, m, 12265 2H; 1.32, d, 3H; 1.28, m, 3H; 0.88, m, 2H.

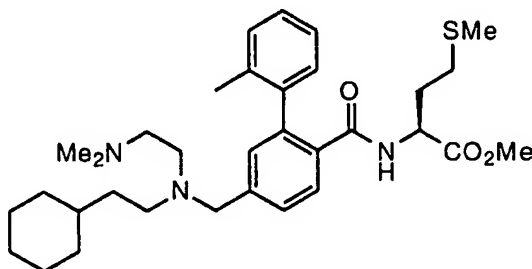
MS (ESI+): 571 (MH⁺); (ESI-): 569 (M-H). Calc'd for C₃₂H₄₆N₂O₃S₂; C 67.33; H 8.12; N 4.91; Found: C 67.12; H 8.10; N 4.70.



12270

Example 1107

N-[4-(N-(2-cyclohexylethyl)-N-2,N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine



12275

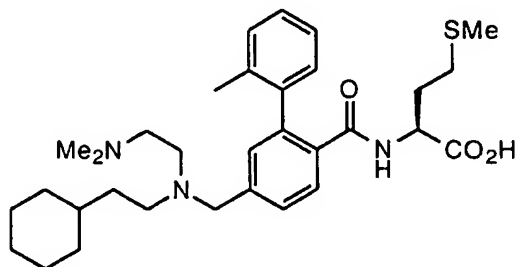
Example 1107A

N-[4-(N-(2-cyclohexylethyl)-N-2,N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

12280 Part 1. Following the procedure of example 1106D, part 1, example 403G (550 mg, 1.43 mmol) and 2-N,N-dimethylaminoethylamine (0.31 mL, 2.86 mmol) and acetic acid (0.82 mL, 14.3 mmol) gave the corresponding secondary amine (673 mg).

Part 2. Following the procedure of example 1106D part 2, the amine produced in example 1107A, part 1 (660 mg, 1.44 mmol) and 2-cyclohexylacetaldehyde (364 mg, 2.88 mmol) gave a material that was purified by column chromatography on silica gel (25 g, ethyl

- 12285 acetate then 90/10/0.1 ethyl acetate/methanol/conc. aq. ammonia) providing 498 mg (60% overall) of the title compound.
¹H NMR (300 MHz., CDCl₃): δ 7.90, dd, 1H; 7.41, dd, 1H; 7.18 - 7.34, m, 4H; 7.16, bs, 1H; 5.88, bs, 1H; 4.62, m, 1H; 3.65, s, 3H; 3.63, s, 2H; 2.57, m, 2H; 2.47, m, 2H; 2.39, m, 2H; 2.21, s, 6H; 1.99, 2.28, m, 7H; 1.86, m, 1H; 1.63, bm, 6H; 1.35, m, 2H; 1.20 m, 2H; 1.14, m, 2H; 0.85, m, 2H.
 12290 MS (ESI+): 568 (MH+); (ESI-): 566 (M-H).



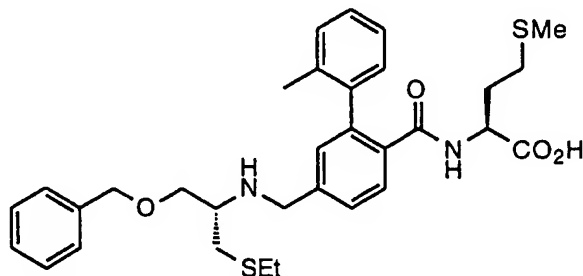
Example 1107B

- 12295 N-[4-(N-(2-cyclohexylethyl)-N-2-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104D, example 1107A (485 mg, 0.85 mmol) provided 382 mg (81%) of the title compound as a white lyophilate.

- ¹H NMR (300 MHz., CD₃OD): δ 7.66, d, 1H; 7.46, d, 1H; 7.05 - 7.33, m, 5H; 4.35, m, 1H; 3.74, s, 2H; 3.17, t, 1H; 2.82, t, 2H; 2.75, s, 6H; 2.60, m, 2H; .24, bs, 1H; 1.94 - 2.12, m, 6H; 1.85, m, 2H; 1.67, m, 6H; 1.45, m, 2H; 1.21, m, 4H; 0.92, m, 2H.
 12300 MS (ESI+): 554 (MH+); (ESI-): 552 (M-H). Calc'd for C₃₂H₄₇N₃O₃S•1.00 H₂O; C 67.22; H 8.64; N 7.35; Found: C 67.23; H 8.43; N 7.26.

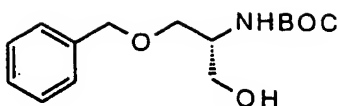
12305



Example 1108

- N-[4-(N-(1-benzyloxymethyl)-2(S)-ethylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

12310

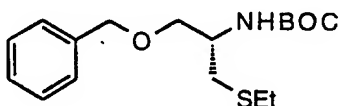
Example 1108A1-benzyloxy-2(S)-t-butoxycarbonylamino-3-hydroxypropane

12315 N-BOC-O-benzylserine (5.0 g, 16.9 mmol) in 30 mL dimethoxyethane was treated with 4-methylmorpholine (2.0 mL, 18.6 mmol) and cooled to 0°C. The solution was treated with isobutylchloroformate (2.3 mL, 17.8 mmol) and the resulting suspension stirred for 15 minutes, then filtered. The solids collected were washed with 2 portions of dimethoxyethane and the washings combined with the original filtrate. This material was cooled in an ice bath and treated with a cold solution of sodium borohydride (1.93 g, 50.8 mmol) in 40 mL 1/2

12320 saturated sodium bicarbonate and the reaction stirred for 2 hours. The mixture was diluted with water and extracted with 3 portions of ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, water and brine, dried, filtered and concentrated to provide the title compound.

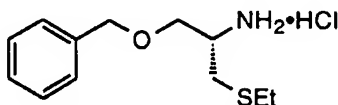
MS (DCI, NH₃): 282 (MH⁺); 299 (M+NH₄)⁺.

12325

Example 1108B1-benzyloxy-2(S)-t-butoxycarbonylamino-3-ethylthiopropene

12330 Following the procedure described in example 1106B (and substituting potassium thioethoxide for sodium thiomethoxide), example 1108A (322 mg, 1.5 mmol) was converted to 342 mg (70% overall) the title compound.

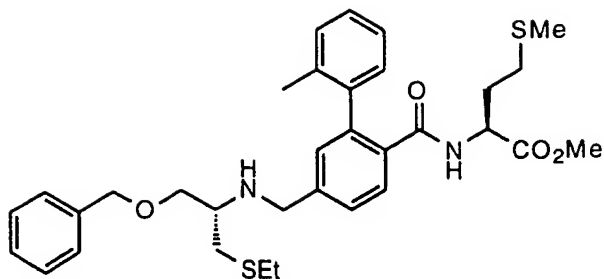
MS (DCI, NH₃): 326 (MH⁺); 343 (M+NH₄)⁺.

Example 1108B1-benzyloxy-2(S)-amino-3-ethylthiopropene hydrochloride salt

12335 Following the procedure described in example 1106C, example 1108B (342 mg, 1.05 mmol) was converted to 244 mg (89%) of the title compound.

MS (DCI, NH₃): 226 (MH⁺).

12340

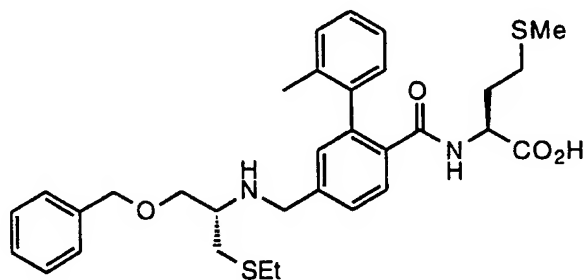


Example 1108C

N-[4-(N-(1-benzyloxymethyl-2(S)-ethylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

12345 Following the procedure described in example 1106D, part 1, example 1108C (144 mg, 0.55 mmol), example 403G (192 mg, 0.50 mmol), diisopropylethylamine (0.098 mL, 0.55 mmol) and acetic acid (0.14 mL, 2.5 mmol) and sodium triacetoxymethylborohydride (213 mg, 1.0 mmol) provided 196 mg (66%) of the title compound after chromatography (silica gel, 20 g, 50% ethyl acetate/hexanes).

12350 MS (ESI+): 595 (MH+); (ESI-): 593 (M-H).



Example 1108D

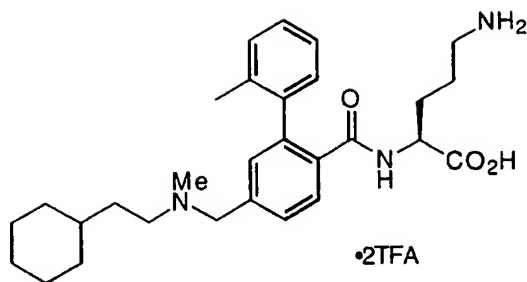
N-[4-(N-(1-benzyloxymethyl-2(S)-ethylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

12355 Following the procedure of example 1104D, example 1108C (187 mg, 0.31 mmol) provided 175 mg of the title compound.

¹H NMR (300 MHz., CD₃OD): δ 7.70, d, 1H; 7.50, d, 1H; 7.08 - 7.39, m, 10H; 4.59, s, 2H; 4.29, m, 1H; 4.20, s, 2H; 3.70, d, 2H; 3.37, m, 1H; 2.85, d, 2H; 2.49, m, 2H; 2.21, bs, 1.5H; 2.08, s, 1.5H; 2.03, m, 1H; 1.98, s, 3H; 1.87, m, 2H; 1.68, m, 1H; 1.20, t, 3H.

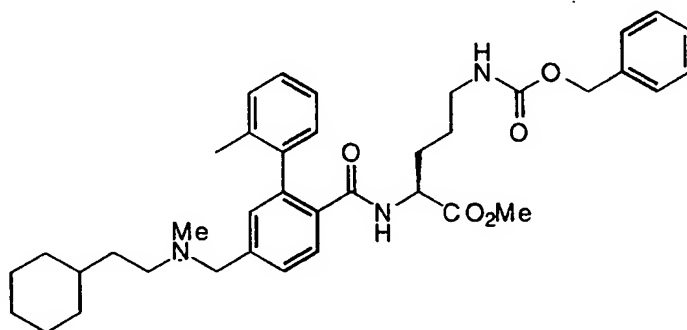
12360 MS (ESI+): 581 (MH+); (ESI-): 579 (M-H). Calc'd for C₃₂H₄₀N₃O₄S₂; C 66.18; H 6.94; N 4.82; Found: C 65.52; H 6.76; N 4.58.

12365

Example 1110

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]ornithine,
Trifluoroacetate salt

12370

Example 1110A

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]-N'-
carbobenzyloxyornithine, Methyl Ester

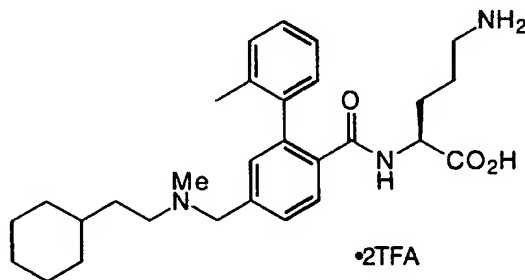
12375

The title compound was prepared according to the procedure in example 608D, replacing L-methionine methyl ester·HCl with L-N'-carbobenzyloxyornithine methyl ester·HCl, and was isolated as a colorless oil.

MS (ESI(+)) m/e 628 (M+H)⁺.

MS (ESI(-)) m/e 626 (M-H)⁻.

12380

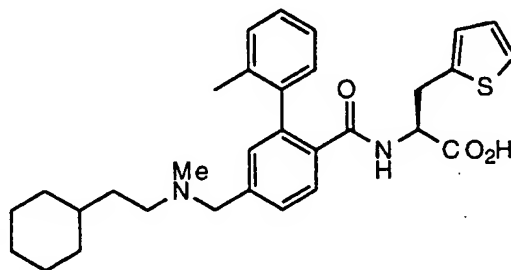
Example 1110B

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]ornithine,
Trifluoroacetate salt

To a solution of N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]-N'-carbobenzyloxyornithine methyl ester (270mg) in methanol (1.4mL) was added 5M LiOH (0.103mL). After 4h, the reaction was concentrated and the residue was dissolved in ethanol (3mL), followed by the addition of freshly distilled cyclohexene (0.1mL), then 10% palladium on carbon (50mg). The reaction vessel was tightly sealed and warmed to 80°C for 1h. Analytical HPCL analysis indicates ca. 30% conversion to the title compound. The reaction was filtered and concentrated, and the hydrogenation protocol was repeated twice. Analytical HPCL analysis of the resulting mixture still indicated low conversion. The reaction was filtered and concentrated, and the residue was dissolved in a minimum of 10% methanol/water, and purified by preparative reverse-phase medium pressure liquid chromatography, eluting with a gradient of methanol/water/0.1%TFA. Lyophilization of the appropriate fractions afforded the title compound as a light yellow powder (38mg).

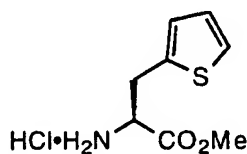
¹H NMR (300 MHz, DMSO) δ 0.83-0.97 (m, 2H), 1.08-1.83 (m, 15H), 2.07-2.14 (m, 4H), 2.62-2.73 (m, 4H), 2.95-3.24 (m, 2H), 4.09-4.17 (m, 1H), 4.22-4.49 (m, 2H), 7.09-7.27 (m, 4H), 7.40 (s, 1H), 7.54-7.73 (m, 5H), 8.40 (brd, J=5 Hz, 1H), 9.68 (brs, 1H).

MS (APCI(-)) m/e 478 (M-H).



Example 1112

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]thien-2-ylalanine

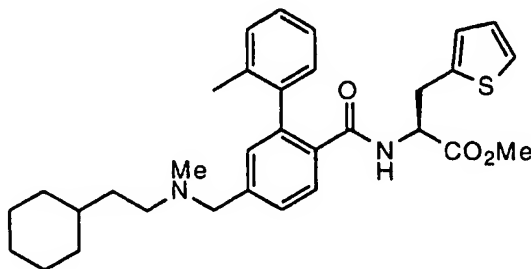


Example 1112A

3-(2-thienyl)-L-alanine, methylester hydrochloride

A solution of 3-(2-thienyl)-L-alanine (200 mg, 1.17 mmol) in 3 mL of methanol was treated with chlorotrimethylsilane (0.73 mL, 5.84 mmol) and the mixture heated to reflux for 60 hours. The solution was then concentrated to provide 257 mg (99%) of the title compound.

MS (DCI, NH₃): 186 (MH⁺); 203 (M+NH₄)⁺.

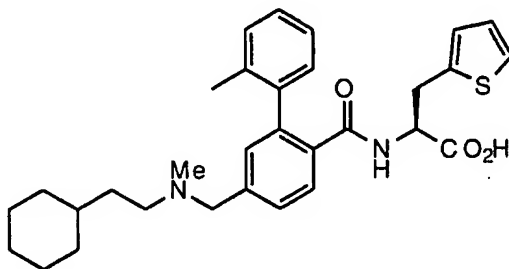


Example 1112B

N-[4-(N-(2-cyclohexylethyl)-N-2-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]thien-2-ylalanine

Following the procedure of example 608D, example 1112A (122 mg, 0.55 mmol) and example 608C (183 mg, 0.5 mmol) were converted to 154 mg (58%) of the title compound.

MS (ESI⁺): 533 (MH⁺); (ESI⁻): 531 (M-H).



Example 1112C

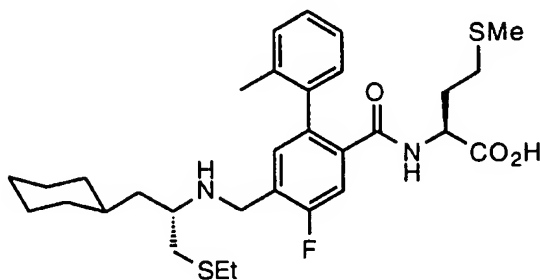
N-[4-(N-(2-cyclohexylethyl)-N-2-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]thien-2-ylalanine

Following the procedure of example 1105D, example 1112C (150 mg, 0.28 mmol) provided 124 mg (85%) of the title compound.

¹H NMR (300 MHz., CD₃OD): δ 7.69, m, 1H; 7.52, dd, 1H; 7.31, bs, 1H; 7.21, m, 2H; 7.14, m, 3H; 6.85, bt, 1H; 6.72, m, 1H; 4.40, m, 1H; 4.24, bd, 2H; 3.10 - 3.27, m, 2H; 3.06, m, 2H; 2.72, s, 3H; 2.08, s, 3H; 1.56 - 1.76, m, 7H; 1.13 - 1.37, m, 4H; 0.96, m, 2H.

MS (ESI+): 519 (MH+); (ESI-): 517 (M-H). Calc'd for $C_{31}H_{38}N_2O_3S \cdot 0.75 H_2O$; C 69.96; H 7.48; N 5.26; Found: C 70.01; H 7.38; N 5.19.

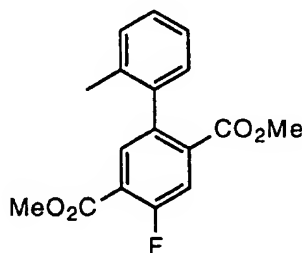
12440



Example 1134

N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-fluoro-2-(2-methylphenyl)benzoyl]methionine

12445



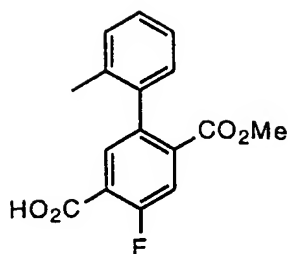
Example 1134A

Dimethyl 2-(2-Methylphenyl)-5-fluoroterephthalate

12450 A stirred solution of the product from example 319B (2.99 g, 10.00 mmol) in 30 ml of dioxane was cooled in an ice bath and 6.5 ml of a 48% aqueous solution of tetrafluoroboric acid was added. The resulting solution was treated with t-butyl nitrite such that the internal temperature did not exceed 10°C and stirring was continued for 30 minutes further. The mixture was carefully diluted with ether (~200 mL) and the solid collected by

12455 filtration. The dried solid was suspended in 20 mL of isooctane and heated to reflux overnight and then diluted with 5 mL of dioxane and heating continued for 1 hour more. The resulting dark mixture was cooled to ambient temperature and concentrated. The residue was purified by column chromatography on silica gel (50g, 5% ethyl acetate/hexanes) to provide 0.87 g (29%) of the title compound.

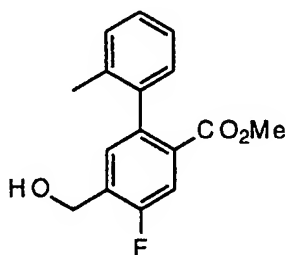
12460 1H NMR (300 MHz., $CDCl_3$): δ 7.73, d, 1H; 7.72, d, 1H; 7.15 - 7.32, m, 3H; 7.06, d, 1H; 3.94, s, 3H; 3.65, s, 3H; 2.07, s, 3H.
MS (DCI- NH_3): 320 (M+ NH_4H^+).

Example 1134B2-(2-Methylphenyl)-4-carboxy-5-fluorobenzoic acid, methyl ester

A solution of example 1134A (0.87 g, 2.88 mmol) in 10 mL of 4:1 THF/methanol was treated with 3 mL of 1M aqueous lithium hydroxide and the mixture stirred at ambient temperature for 60 hours. The solution was made acidic by the addition of excess 3N aqueous HCl and then extracted with 3 portions of ethyl acetate. The combined organic extracts were washed with water and brine, dried, filtered and concentrated to provide 0.77 g (92%) of the title compound sufficiently pure to use in the next step.

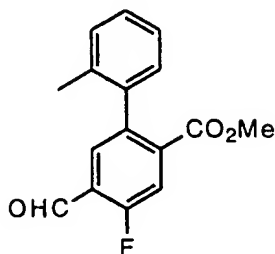
¹H NMR (300 MHz, CD₃OD): δ 7.74, d, 1H; 7.69, d, 1H; 7.15 - 7.28, m, 3H; 7.03, q, 1H; 3.61, s, 3H; 2.07, s, 3H.

MS (DCI, NH₃): 306 (M+ NH₄⁺).

Example 1134C2-(2-Methylphenyl)-4-hydroxymethyl-5-fluorobenzoic acid, methyl ester

A solution of example 1134B (760 mg, 2.64 mol) in 5 mL of dimethoxyethane was treated with 4-methylmorpholine (0.32 mL, 2.90 mmol) and the mixture cooled in an ice bath. The clear solution was then treated with isobutylchloroformate (0.36 mL, 2.77 mmol) and the suspension stirred for 30 minutes. The mixture was filtered and the solids washed with 2 portions of THF and the combined filtrates recooled in an ice bath. The cold solution was treated with a mixture of sodium borohydride (300 mg, 7.92 mmol) in 3 mL of 1/2 saturated sodium bicarbonate and the mixture stirred for 2 hours. The mixture was diluted with water and extracted with 3 portions of ethyl acetate. The combined organic extracts were washed with water and brine, dried, filtered and concentrated. The residue was purified by column chromatography of silica gel (35 g, 25% ethyl acetate/hexanes) to provide 527 mg (73%) of the title compound.

^1H NMR (300 MHz., CDCl_3): δ 7.67, d, 1H; 7.44, d, 1H; 7.15 - 7.28, m, 3H; 7.05, d, 1H; 4.83, d, 1H; 3.62, s, 3H; 2.07, s, 3H; 1.94, bt, 1H.
MS (DCI, NH_3): 292 ($\text{M} + \text{NH}_4^+$).



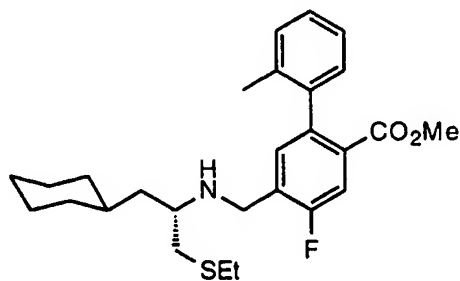
Example 1134D

2-(2-Methylphenyl)-4-formyl-5-fluorobenzoic acid, methyl ester

A stirred solution of example 1134C (515 mg, 1.79 mmol) in 2 mL of methylene chloride was treated with KBr (21 mg, 0.18 mmol), 2 mL of water and sodium bicarbonate (0.5 g) and then cooled in an ice bath. The mixture was treated with TEMPO (3 mg, 0.02 mmol) and then commercial bleach (Chlorox, 3.1 mL) was added such that the temperature did not exceed 5°C . The mixture was stirred for 10 minutes at which time an additional 1.5 mL of Chlorox was added. After stirring a further 10 minutes, the mixture was diluted with water and layers were separated. The aqueous phase was extracted with 1 portion of methylene chloride and the combined organic phases were extracted with 5% aqueous sodium bisulfite, dried, filtered and concentrated to give 478 mg (93%) of the title compound.

^1H NMR (300 MHz., CDCl_3): δ 10.43, s, 1H; 7.77, d, 1H; 7.73, d, 1H; 7.17 - 7.31, m, 3H; 7.05, m, 1H; 3.63, s, 3H; 2.06, s, 3H.

MS (DCI, NH_3): 290 ($\text{M} + \text{NH}_4^+$).



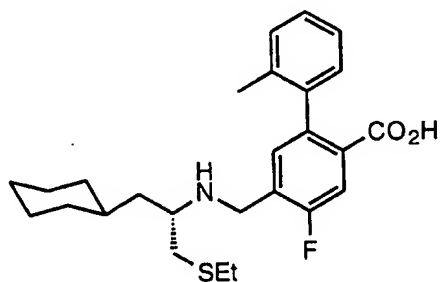
Example 1134E

N-[4-(1-ethylthio-3-cyclohexyl)prop-2-ylaminomethyl]-5-fluoro-2-(2-methylphenyl)benzoic acid methyl ester

Example 1134D (143 mg, 0.5 mmol) was dissolved in 2 mL of 1,2-dichloroethane and the amine hydrochloride salt from example 403D (178 mg, 0.75 mmol), diisopropylethylamine (0.13 mL, 0.75 mmol) and acetic acid (0.15 mL, 2.50 mmol) were sequentially added. The mixture was stirred at ambient temperature for 4 hours and then treated with sodium triacetoxyborohydride (213 mg, 1.0 mmol) and the mixture stirred overnight. The reaction was quenched by the addition of 2 mL of 2M aqueous sodium carbonate and the mixture stirred vigorously for 1 hour and then diluted with water and methylene chloride. The aqueous layer was extracted with methylene chloride and the combined organic layers dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (20g, 15% ethyl acetate/hexanes) to provide 165 mg (72%) of the title compound.

¹H NMR (300 MHz, CDCl₃): δ 7.67, d, 1H; 7.16 - 7.31, m, 5H; 7.04, bd, 1H; 3.93, s, 2H; 3.63, s, 3H; 2.76, m, 2H; 2.57, m, 1H; 2.46, q, 2H; 2.06, s, 3H; 1.63, bm, 6H; 1.37, bm, 3H; 1.22, t, 3H; 1.13, m, 2H; 0.87, m, 2H.

MS (ESI +): 458 (MH⁺); (ESI-) 456 (M-H).

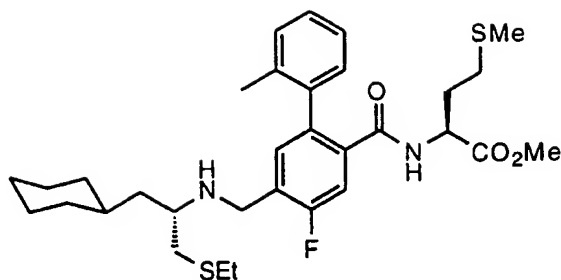


Example 1134F

N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-fluoro-2-(2-methylphenyl)benzoic acid

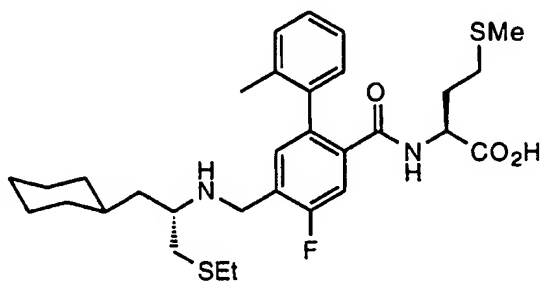
Example 1134E (160 mg, 0.35 mmol) was dissolved in 1.5 mL of ethanol and aqueous sodium hydroxide was added (1.75 mL of a 4N solution) and the mixture heated to reflux for 3 hours. The cooled solution was concentrated to dryness and dissolved in water and the pH adjusted to ~ 4 with 1M aqueous phosphoric acid. The mixture was extracted with 3 portions of ethyl acetate and the combined organic extracts were washed with brine, dried, filtered and concentrated to provide 164 mg (105%) of the title compound.

¹H NMR (300 MHz, CD₃OD): δ 7.78, d, 1H; 7.43, d, 1H; 7.15 - 7.27, m, 3H; 7.06, bd, 1H; 4.42, m, 2H; 3.48, m, 1H; 3.00, dd, 1H; 2.93, dd, 1H; 2.58, q, 2H; 2.09, s, 3H; 1.63 - 1.79, m, 7H; 1.45, bm, 2H; 1.14 - 1.36, m, 6H; 0.84 - 1.09, m, 2H.

Example 1134G

N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-fluoro-2-(2-methylphenyl)benzoyl]methionine, methyl ester

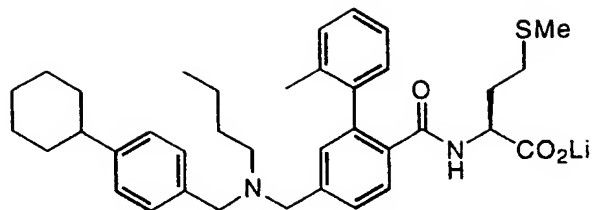
12550 According to the procedure described in example 1178I, example 1134F (160 mg, 0.35 mmol) provided 140 mg (68%) of the title compound after column chromatographic purification on silica gel (20 g, 35% ethyl acetate/hexanes).
¹H NMR (300 MHz., CDCl₃): δ 7.70, dd, 1H; 7.14 - 7.38, m, 5H; 5.91, bd, 1H; 4.60, m, 1H; 3.94, s, 2H; 3.66, s, 3H; 2.77, m, 2H; 2.58, m, 1H; 2.46, q, 2H; 2.28, s, 1.5 H(o-tolyl rotamer); 2.07, s, 1.5H (o-tolyl rotamer); 1.95 - 2.10, m, 5H; 1.84, m, 2H; 1.50 - 1.72, m, 6H; 1.26 - 1.48, m, 3H; 1.21, t, 3H; 1.04 - 1.26, m, 3H; 0.88, m, 2H. MS: (ESI⁻): 587 (M-H).

Example 1134H

N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-fluoro-2-(2-methylphenyl)benzoyl]methionine

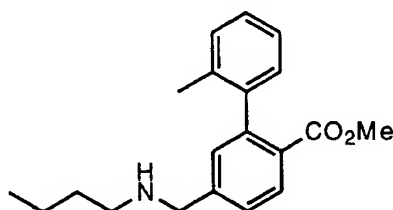
Following the procedure of example 1105D, example 1134G (130 mg, 0.22 mmol) provided 94 mg (75%) of the title compound.

12565 ¹H NMR (300 MHz., CD₃OD): δ 7.52, d, 1H; 7.39, m, 1H; 7.10 - 7.30, m, 4H; 4.29, m, 1H; 4.25, q, 2H; 3.24, m, 1H; 2.89, dd, 1H; 2.78, dd, 1H; 2.52, q, 2H; 2.22, bs, 1.5H; 2.08, bs, 1.5H; 2.05, m, 1H; 1.98, s, 3H; 1.89, m, 2H; 1.69, m, 6H; 1.58, t, 2H; 1.43, m, 1H; 1.25, m, 1H; 1.22, t, 3H; 0.90, m, 2H.
 MS (ESI⁺): 575 (MH⁺): (ESI⁻): 573 (M-H). Calc'd for C₃₁H₄₃FN₂O₃S₂•0.35 H₂O; C 64.07; H 7.58; N 4.82; Found: C 64.08; H 7.54; N 4.65.



Example 1136

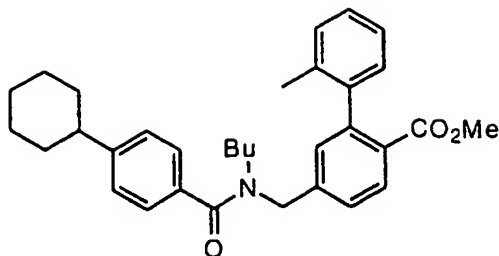
N-[4-(N-butyl-N-4-cyclohexylbenzylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt



Example 1136A

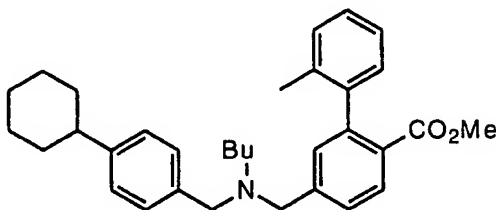
Methyl 4-(N-Butylaminomethyl)-2-(2-methylphenyl)benzoate

To a 0 °C solution of intermediate 1178B (1.0 g, 3.71 mmol) in DCM (10 mL) was added oxalyl chloride (2.0 M in DCM, 3.7 mL), and a drop of DMF. The reaction was stirred at room temperature for 2 hours, and was then evaporated to dryness. The residue was redissolved in DCM (10 mL), and was cooled to 0 °C. To it was slowly added butylamine (0.5 mL). The reaction mixture was stirred for 5 min., and then was filtered through silica gel (10 g), rinsed with ethyl acetate, and concentrated. The solid was dissolved in THF (10 mL), and to it was added borane (1.0 M in THF, 5.0 mL), and the reaction mixture was refluxed for 15 hours. Methanol (0.5 mL) was added dropwisely to the reaction, followed by concentrated HCl (1 mL), and the mixture was heated at 60 °C for 1 hour. Then it was cooled to room temperature, the reaction mixture was adjusted to pH about 12-14 with sodium carbonate (2.0 M in water). The reaction mixture was then partitioned between ethyl acetate (50 mL) and water (5 mL). The organic layer was washed with water (10 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to give the intermediate amine. The amine was used without further purification.

Example 1136BMethyl 4-[N-butyl-N-(4-cyclohexylbenzyl)aminomethyl]-2-(2-methylphenyl)benzoate

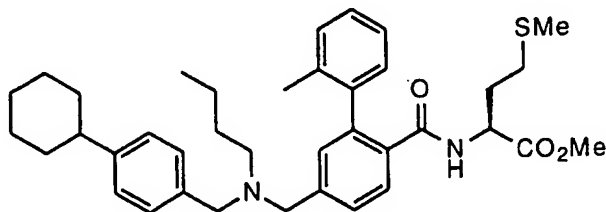
To a 0 °C solution of 4-cyclohexylbenzoic acid (204 mg, 1.0 mmol) in DCM (3 mL) was added oxalyl chloride (2.0 M in DCM, 1.0 mL), and a drop of DMF. The reaction was stirred at room temperature for 2 hours, and was then evaporated to dryness. The residue was redissolved in DCM (10 mL), and was cooled to 0 °C. To it was slowly added the intermediate 1136A (156 mg, 0.5 mmol) and triethylamine (202 mg, 2.0 mmol) in DCM (3 mL). The reaction mixture was stirred for 5 min., and then was filtered through silica gel (10 g), rinsed with ether, and concentrated. The residue was purified by column chromatography with 20% ethyl acetate in to give the title compound (165 mg, 66%).

¹HNMR (300 MHz, CDCl₃) δ 7.95 (d, 1 H), 7.32-7.16 (m, 9 H), 7.05 (br d, 1 H), 5.85-5.55 (loop, 2 H), 3.61 (s, 3 H), 3.47-3.17 (broad loop, 2 H), 2.49 (m, 1 H), 2.06 (s, 3 H), 1.90-0.70 (m, 17 H). MS(CI/NH₃) m/z: 498 (M+H)⁺.

Example 1136CMethyl 4-(N-Butyl-N-4-cyclohexylbenzylaminomethyl)-2-(2-methylphenyl)benzoate

To a solution of intermediate 1136B (93 mg) in THF (2 mL) was added borane (1.0 M in THF, 1.0 mL), and the reaction mixture was refluxed for 15 hours. Methanol (0.5 mL) was added dropwisely to the reaction, followed by concentrated HCl (0.5 mL), and the mixture was heated at 60 °C for 1 hour. Then it was cooled to room temperature, and was adjusted to pH about 12-14 with sodium carbonate (2.0 M in water). The reaction mixture was then partitioned between ethyl acetate (50 mL) and water (5 mL). The organic layer was washed with water (10 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to give the title amine (88 mg, 94%). ¹HNMR (300 MHz, CDCl₃)

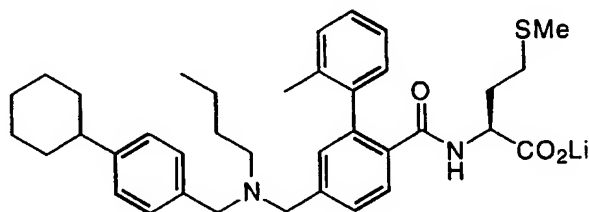
12625 δ 7.90 (d, 1 H), 7.42 (dd, 1 H), 7.30-7.15 (m, 4 H), 7.12 (m, 2 H), 7.06 (m, 1 H), 3.59 (s, 2 H), 3.57 (br s, 2 H), 3.53 (br s, 2 H), 2.47 (m, 1 H), 2.41 (t, 2 H), 2.05 (s, 3 H), 1.90-1.20 (m, 14 H), 0.94 (t, 3 H). MS(CI/NH₃) m/z: 484 (M+H)⁺.



Example 1136D

12630 N-[4-(N-Butyl)-N-4-cyclohexylbenzylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine Methyl Ester

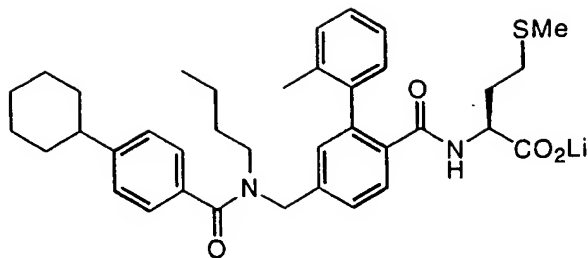
The procedures described in the Example 403E and 403F were used here to convert above intermediate 1136C (85 mg) to the title methyl ester 1136D (73 mg, 68%). ¹H NMR (300 MHz, CDCl₃) δ 7.90 (2 d's 1 H), 7.45 (br d, 1 H), 7.35-7.22 (m, 6 H), 7.19 (br s, 1 H), 7.13 (br d, 2 H), 5.85 (m, 1 H), 4.62 (m, 1 H), 3.65 (s, 3 H), 3.57 (s, 2 H), 3.53 (s, 2 H), 2.48 (m, 1 H), 2.41 (t, 2 H), 2.20-2.00 (4 s's, 6 H), 2.05 (m, 2 H), 1.92-1.20 (m, 16 H), 0.82 (t, 3 H). MS(CI/NH₃) m/z: 615 (M+H)⁺.



Example 1136E

12640 N-[4-(N-butyl-N-4-cyclohexylbenzylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

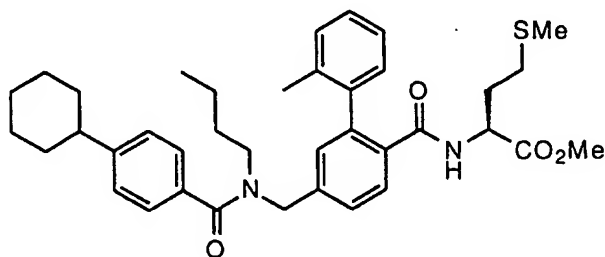
The procedure described in the Example 403I was used here to convert the intermediate 1136D (64 mg) to the title lithium salt (64 mg, 100%). ¹H NMR (300 MHz, dmso-d₆) δ 7.49 (d, 1 H), 7.37 (br d, 1 H), 7.25-7.09 (m, 9 H), 6.91 (d, 1 H), 3.63 (m, 1 H), 3.56 (br s, 2 H), 3.47 (br s, 2 H), 2.45 (m, 1 H), 2.37 (t, 2 H), 2.17-1.98 (m, 8 H), 1.81-1.17 (m, 16 H), 0.76 (t, 3 H). MS(ESI-) m/z: 599 (M-H)⁻.



12650

Example 1137

N-[4-(N-Butyl-N-4-cyclohexylbenzoylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt



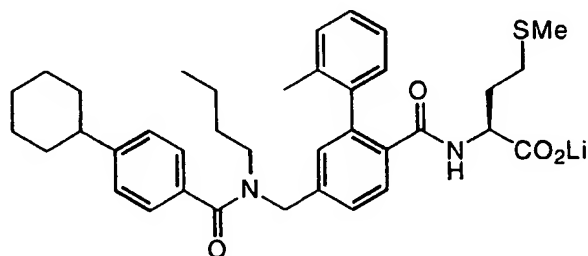
12655

Example 1137A

N-[4-(N-butyl-N-4-cyclohexylbenzoylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine
Methyl Ester

The procedures described in the Example 403E and 403F were used here to convert intermediate 1136B (63 mg) to the title methyl ester 1137A (72 mg, 90%). ¹HNMR (300 MHz, CDCl₃) δ 7.94 (2 d's 1 H), 7.37-7.15 (m, 10 H), 5.89 (m, 1 H), 4.80 (m, 1 H), 4.61 (br. loop, 2 H), 3.66 (s, 3 H), 3.43, 3.22 (2 br loops, 2 H), 2.50 (m, 1 H), 2.20-2.00 (m, 8 H), 1.92-1.00 (m, 16 H), 0.96-0.70 (2 br loops, 3 H). MS(CI/NH₃) m/z: 629 (M+H)⁺.

12660



12665

Example 1137B

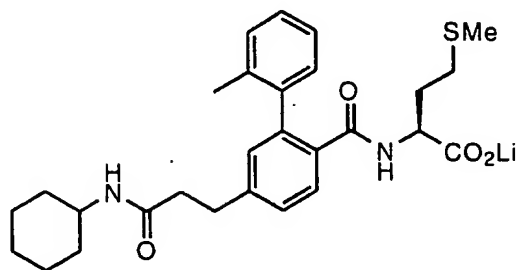
N-[4-(N-Butyl-N-4-cyclohexylbenzoylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The procedure described in the Example 403I was used here to convert the intermediate 1137B (68 mg) to the title lithium salt (67 mg, 100%). ¹H NMR (300 MHz,

12670

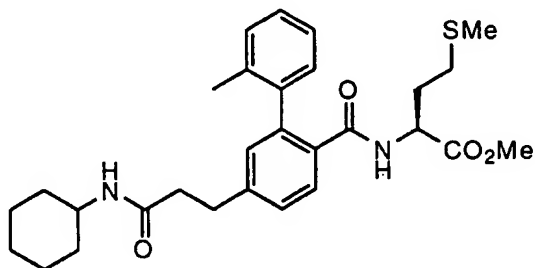
dmso-d₆) δ 7.53 (br d, 1 H), 7.42-7.08 (m, 9 H), 6.97 (m, 1 H), 6.95 (br d, 1 H), 4.72, 4.57 (2 br. loops, 2 H), 3.65 (m, 1 H), 3.17 (br loop, 2 H), 2.50 (m, 1 H), 2.20-1.88 (m, 8 H), 1.86-0.95 (m, 16 H), 0.88, 0.67 (2 br loops, 3 H). MS(ESI-) m/z: 613 (M-H)⁻

12675

Example 1139

N-[4-(N-Cyclohexylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

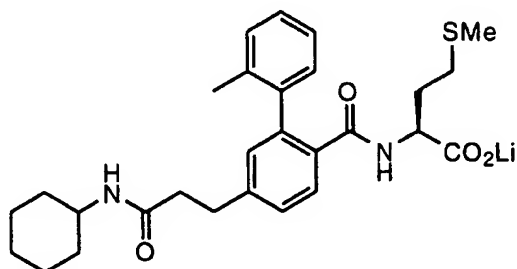
12680

Example 1139 A

N-[4-(N-Cyclohexylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

The procedures described in the Example 403E and 403F were used here to convert intermediate 1144C (127 mg) to the title methyl ester (141 mg, 83%). ¹HNMR (300 MHz, CDCl₃) δ 7.89 (2 d's, 1 H), 7.32-7.24 (m, 4 H), 7.95 (br d, 1 H), 7.03 (br s, 1 H), 5.86 (br d, 1 H), 5.16 (m, 1 H), 4.62 (m, 1 H), 3.75 (m, 1 H), 3.02 (t, 2 H), 2.45 (t, 2 H), 2.20-2.00 (m, 8 H), 1.92-0.97 (m, 12 H).

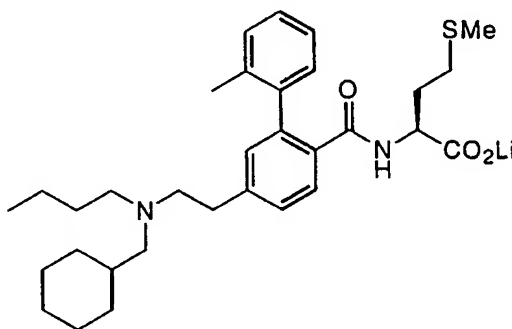
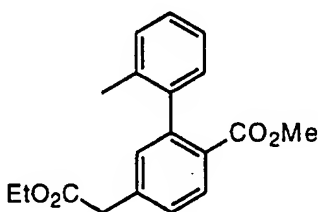
12685



12690

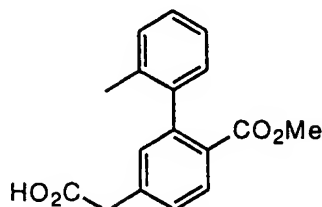
Example 1139BN-[4-(N-Cyclohexylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

The procedure described in the Example 403I was used here to convert the intermediate 1139A (134 mg) to the title lithium salt (121 mg, 93%). ¹H NMR (300 MHz, dms_o-d₆) δ 7.67 (d, 1 H), 7.45 (d, 1 H), 7.27-7.08 (m, 5 H), 6.97 (m, 1 H), 6.88 (m, 1 H), 3.66 (m, 1 H), 2.85 (t, 2 H), 2.36 (t, 2 H), 2.00-1.90 (m, 8 H), 1.88-0.98 (m, 12 H). MS(ESI⁻) m/z: 495 (M-H)⁻.

Example 1140N-[4-(N-cyclohexylmethyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine lithium saltExample 1140AMethyl 4-(Ethoxycarbonylmethyl)-2-(2-methylphenyl)benzoate

A solution of intermediate 1178D (397 g, 1.24 mmol), palladium(II) acetate (22 mg), 1,3-bis(diphenylphosphino)propane (42 mg), N,N-diisopropylethylamine (0.5 mL) in ethanol (1 mL) and DMF (5 mL) was stirred at 80 °C under carbon monoxide balloon for 4 hours. The reaction mixture was then partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with water (2 X 20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 5% ethyl acetate in hexane to give the title compound (233 mg, 58%). ¹HNMR (300 MHz, CDCl₃) δ 7.94 (d, 1 H), 7.35 (dd, 1 H), 7.30-7.17 (m, 3

H), 7.16 (d, 1 H), 7.07 (br d, 1 H), 4.16 (q, 2 H), 3.67 (s, 2 H), 3.61 (s, 3 H), 2.06 (s, 3 H), 1.25 (t, 3 H). MS(CI/NH₃) m/z: 330 (M+NH₄)⁺.

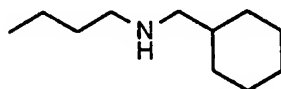


12720

Example 1140BMethyl 4-(Carboxymethyl)-2-(2-methylphenyl)benzoate

To the solution of intermediate 1140A (213 mg, 0.682 mmol) in methanol (3 mL) was added NaOH (0.979 M in water, 0.697 mL). After 2 hours, the reaction mixture was acidified with HCl (1.0 M, 1 mL), and was then partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with water (2 X 20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was used without further purification.

12725

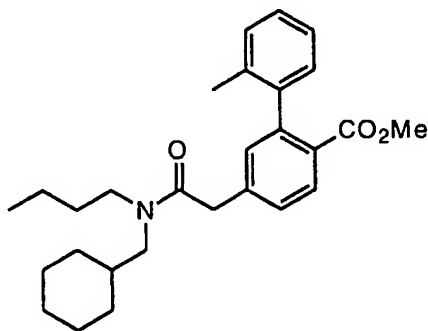


12730

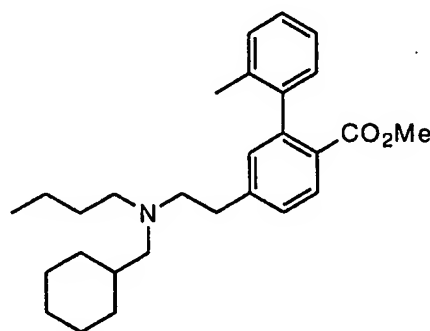
Example 1140CN-Butylcyclohexylmethanamine

The procedures described in the Example 1178E and 1178F were used here to convert cyclohexylacetyl chloride (1.47 g, 10.0 mmol) and butylamine to the title amine in 85% yield. The amine was not purified before it was used.

12735

Example 1140DMethyl 4-(N-Cyclohexylmethyl-N-butylaminocarbonylmethyl)-2-(2-methylphenyl)benzoate

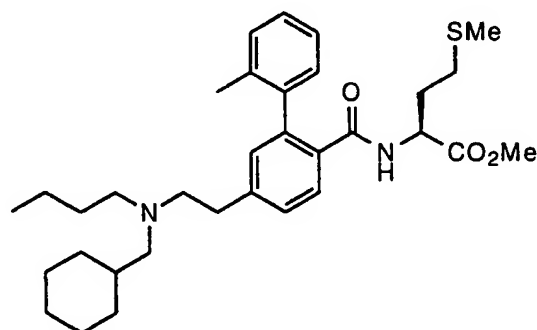
The procedure described in example 1144C was used here to combine intermediate 1140B (311 mg, 1.10 mmol) and intermediate 1140C (205 mg) to give the title compound (247 mg, 52%). ¹HNMR (300 MHz, CDCl₃) δ 7.94 (d, 1 H), 7.33 (M, 1 H), 7.25-7.15 (m, 3 H), 7.13, 7.11 (2 d's, 1 H), 7.05 (m, 1 H), 3.76, 3.75 (2 s's, 2 H), 3.60 (s, 3 H), 3.35-3.05 (m, 4H), 2.05, 2.04 (2 s's, 3 H), 1.80-1.10 (m, 15 H), 0.91, 0.89 (2 t's, 3 H). MS(Cl/NH₃) m/z: 436 (M+H)⁺.



Example 1140E

Methyl 4-(N-Cyclohexylmethyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoate

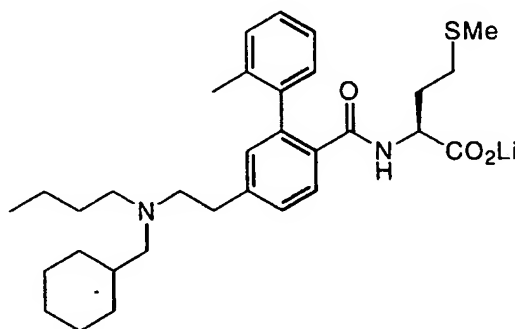
A solution of intermediate 1140D (118 mg, 0.271 mmol) and borane (1.0 M in THF, 0.54 mL) in THF was refluxed for 15 hours. Methanol (0.5 mL) was added dropwisly to the reaction, followed by concentrated HCl (0.5 mL), and the mixture was heated at 60 °C for 1 hour. The it was cooled to room temperature, The reaction mixture was adjusted to pH about 12-14 with sodium carbonate (2.0 M in water). The reaction mixture was then partitioned between ethyl acetate (50 mL) and water (5 mL). The organic layer was washed with water (10 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to give the intermediate amine 1140E. The amine was used without further purification. ¹HNMR (300 MHz, CDCl₃) δ 7.90 (d, 1 H), 7.28-7.17 (m, 4 H), 7.05 (m, 2 H), 3.60 (s, 3 H), 2.75 (m, 2 H), 2.66 (m, 2 H), 2.40 (t, 2 H), 2.19 (d, 2 H), 2.06 (s, 3 H), 1.80-1.10 (m, 15 H), 0.88 (t, 3 H). MS(Cl/NH₃) m/z: 422 (M+H)⁺.



Example 1140FN-[4-(N-Cyclohexylmethyl)-N-butylaminoethyl]-2-(2-methylphenyl)benzoyl]methionineMethyl Ester

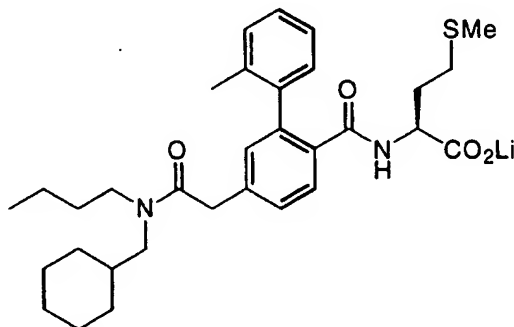
12765 The procedures described in the Example 403E and 403F were used here to convert the above intermediate amine 1140E to the title methyl ester (113 mg, 76%, 3 steps from 1140D). ¹H NMR (300 MHz, CDCl₃) δ 7.90 (2 d's, 1 H), 7.34-7.18 (m, 5 H), 7.01 (s, 1 H), 5.87 (br d, 1 H), 4.62 (m, 1 H), 3.65 (s, 3 H), 2.75 (m, 2 H), 2.66 (m, 2 H), 2.41 (t, 2 H), 2.20 (d, 2 H), 2.19-1.98 (m, 8 H), 1.87 (m, 1 H), 1.80-1.10 (m, 16 H), 0.88 (t, 3 H). MS(CI/NH₃) m/z: 553 (M+H)⁺.

12770

Example 1140GN-[4-(N-cyclohexylmethyl)-N-butylaminoethyl]-2-(2-methylphenyl)benzoyl]methioninelithium salt

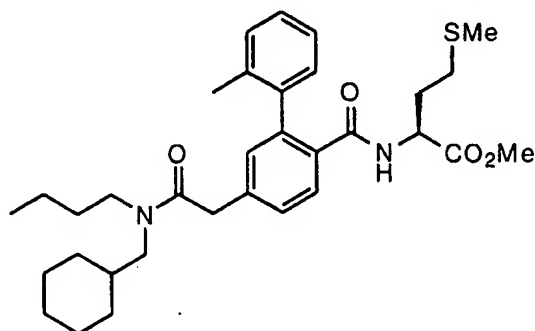
12775 The procedure described in the Example 403I was used here to convert the intermediate 1140F (107 mg) to the title lithium salt (91 mg, 87%). ¹H NMR (300 MHz, dmso-d₆) δ 7.51 (d, 1 H), 7.33-7.13 (m, 5 H), 7.05 (br s, 1 H), 6.95 (m, 1 H), 3.71 (m, 1 H), 2.76 (m, 2 H), 2.67 (m, 2 H), 2.42 (t, 2 H), 2.21 (d, 2 H), 2.10-1.82 (m, 8 H), 1.80-1.10 (m, 17 H), 0.88 (t, 3 H). MS(ESI-) m/z: 537 (M-H)⁻.

12780

Example 1141

12785

N-[4-(N-Cyclohexylmethyl-N-butylaminocarbonylmethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt



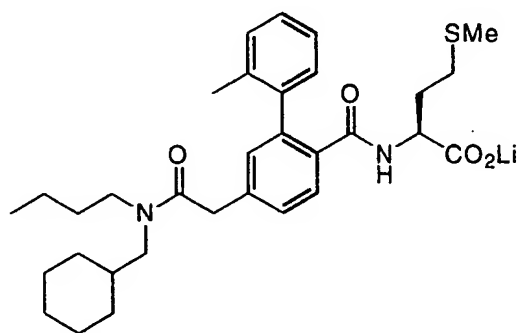
Example 1141A

12790

N-[4-(N-Cyclohexylmethyl-N-butylaminocarbonylmethyl)-2-(2-methylphenyl)benzoyl]methionine Methyl Ester

The procedures described in the Example 403E and 403F were used here to convert the intermediate 1140D (101 mg) to the title methyl ester (127 mg, 97%). ¹HNMR (300 MHz, CDCl₃) δ 7.92 (m, 1 H), 7.37-7.22 (m, 4 H), 7.19 (m, 1 H), 7.11 (br d, 1 H), 5.88 (br d, 1 H), 4.61 (m, 1 H), 3.76, 3.75 (2 s's, 2 H), 3.65 (s, 3 H), 3.37-2.04 (m, 4 H), 2.00-1.97 (m, 8 H), 1.95-1.10 (m, 17 H), 0.92, 0.88 (2 t's, 3 H). MS(CI/NH₃) m/z: 567 (M+H)⁺.

12795



12800

Example 1141B

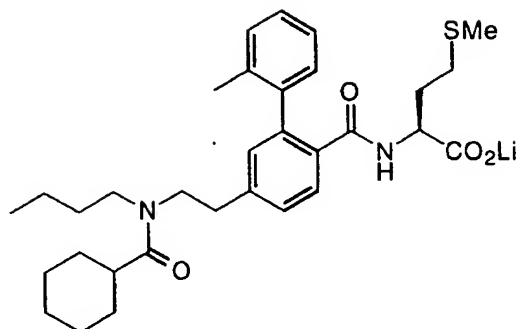
N-[4-(N-Cyclohexylmethyl-N-butylaminocarbonylmethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The procedure described in the Example 403I was used here to convert the intermediate 1141A (119 mg) to the title lithium salt (102 mg, 86%). ¹H NMR (300 MHz, dmso-d₆) δ 7.48 (2 d's, 1 H), 7.30 (m, 1 H), 7.25-7.08 (m, 4 H), 7.03 (br s, 1 H), 5.95 (m, 1 H), 3.74, 3.72 (2 s's, 2 H), 3.69 (m, 1 H), 3.23 (t, 2 H), 3.11 (m, 2 H), 2.20-1.90

12805

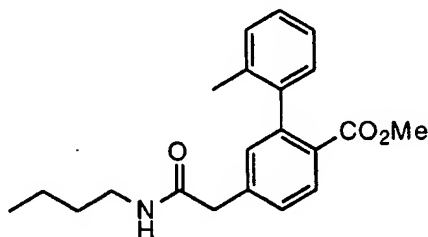
(m, 8 H), 1.85 (m, 1 H),), 1.79-1.00 (m, 17 H), 0.86,0.83 (2 t's, 3 H). MS(ESI-) m/z: 551 (M-H)⁻.

12810

Example 1142

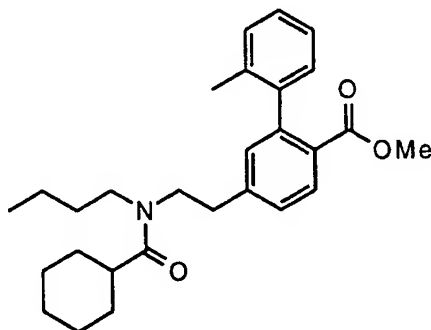
N-[4-(N-Cyclohexanoyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

12815

Example 1142A

Methyl 4-(N-Butylaminocarbonylmethyl)-2-(2-methylphenyl)benzoate

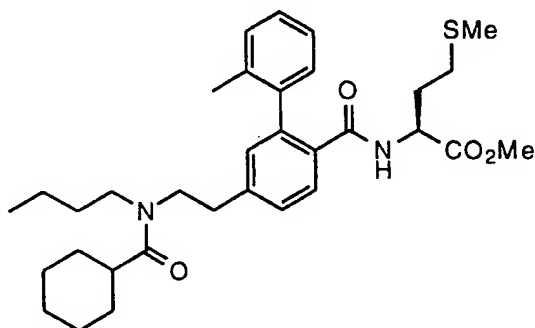
The procedure described in example 1144C was used here to combine intermediate
 12820 1140B (200 mg, 0.70 mmol) and butylamine to give the title compound (171 mg, 69%).
¹HNMR (300 MHz, CDCl₃) δ 7.95 (d, 1 H), 7.34 (dd, 1 H), 7.30-7.17 (m, 3 H), 7.13 (d, 1 H), 7.05 (d, 1 H), 5.36 (m, 1 H), 3.61 (s, 3 H), 3.60 (s, 2 H), 3.24 (q, 1 H), 2.07 (s, 3 H), 1.42 (m, 2 H), 1.27 (m, 2 H), 0.88 (t, 3 H).



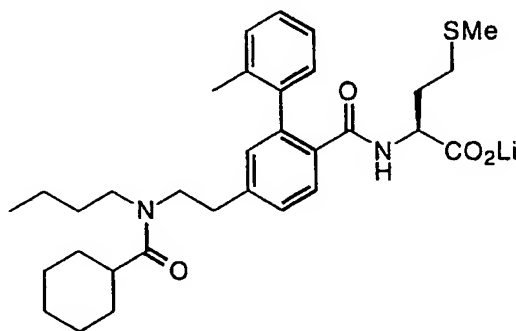
12825

Example 1142BMethyl N-[4-(N-Cyclohexanoyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoate

The procedures described in 1143B was used here to convert 1142A (102 mg, 0.36 mmol) to the title compound (137 mg, 87%). ¹HNMR (300 MHz, CDCl₃) δ 7.92 (2 d's, 1 H), 7.30-7.17 (m, 4 H), 7.05 (m, 2 H), 3.61 (2 s's, 3 H), 3.52 (m, 2 H), 3.07,3.06 (2 t's, 2 H), 2.90 (t, 2 H), 2.37 (m, 1 H), 2.07,2.04 (2s's, 3 H), 2.00-1.15 (m, 14 H), 0.92,0.90 (2 t's, 3 H). MS(CI/NH₃) m/z: 436 (M+H)⁺.

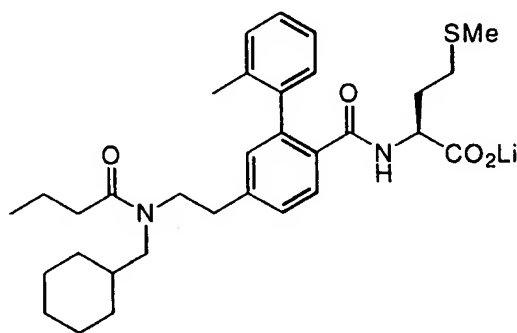
Example 1142CN-[4-(N-Cyclohexanoyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine Methyl Ester

The procedures described in the Example 403E and 403F were used here to convert the above intermediate 1142B (130 mg) to the title methyl ester (112 mg, 66%). ¹HNMR (300 MHz, CDCl₃) δ 7.91 (2 d's, 1 H), 7.37-7.15 (m, 5 H), 7.06,6.99 (2 br s's, 1 H), 6.90 (br d, 1 H), 4.61 (m, 1 H), 3.66,2.65 (2 s's, 3 H), 3.52 (m, 2 H), 3.19,2.92 (2 m's, 4 H), 2.30-2.00 (m, 9 H), 1.86 (m, 1 H), 1.80,1.10 (m, 15 H), 0.94,0.91 (2 t's, 3 H). MS(CI/NH₃) m/z: 567 (M+H)⁺.

Example 1142DN-[4-(N-Cyclohexanoyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

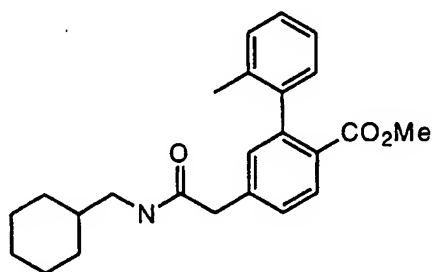
The procedure described in the Example 403I was used here to convert the
 12850 intermediate 1142C (103 mg) to the title lithium salt (99 mg, 97%). ¹H NMR (300 MHz, dms_o-d₆) δ 7.48 (2 d's, 1 H), 7.31-6.86 (m, 7 H), 3.63 (m, 1 H), 3.48 (m, 2 H), 3.10, 2.95 (2 m's, 2 H), 2.82 (2 t's, 2 H), 2.25-1.90 (m, 9 H), 1.80 (m, 1 H), 1.75-1.07 (m, 15 H), 0.84, 0.80 (2 t's, 3 H). MS(ESI-) m/z: 551 (M-H)⁻.

12855

Example 1143

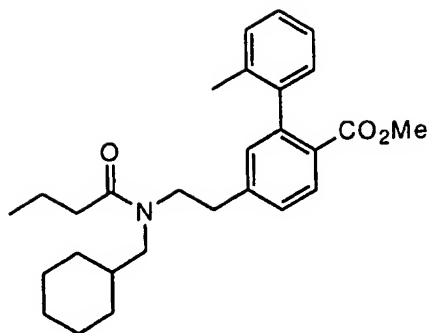
N-[4-(N-Cyclohexylmethyl-N-butanoylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

12860

Example 1143A

Methyl 4-(N-Cyclohexylmethylaminocarbonylmethyl)-2-(2-methylphenyl)benzoate

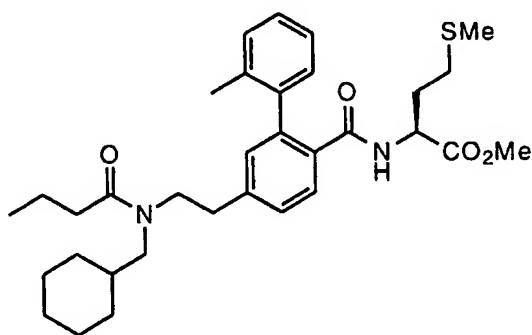
The procedure described in example 1144C was used here to combine intermediate
 12865 1140B (301 mg, 1.05 mmol) and cyclohexylmethylamine to give the title compound (266 mg, 67%). ¹H NMR (300 MHz, CDCl₃) δ 7.97 (d, 1 H), 7.35 (dd, 1 H), 7.27-7.17 (m, 3 H), 7.15 (d, 1 H), 7.05 (d, 1 H), 5.41 (m, 1 H), 3.62 (2 overlapped s's, 5 H), 3.07 (t, 2 H), 2.06 (s, 3 H), 1.85-0.87 (m, 11 H). MS(Cl/NH₃) m/z: 380 (M+H)⁺.



Example 1143B

Methyl 4-(N-Cyclohexylmethyl-N-butanoylaminoethyl)-2-(2-methylphenyl)benzoate

To a solution of intermediate 1143A (108 mg, 0.285 mmol) in THF (2 mL) was added borane (1.0 M in THF, 0.5 mL), and the reaction mixture was stirred at room temperature for 7 hours. Methanol (0.5 mL) was added dropwisly to the reaction, followed by concentrated HCl (0.5 mL), and the mixture was heated at 60 °C for 1 hour. Then it was cooled to room temperature, and was adjusted to pH about 12-14 with sodium carbonate (2.0 M in water). The reaction mixture was then partitioned between ethyl acetate (50 mL) and water (5 mL). While still in the separatory funnel, butyryl chloride (0.5 mL) was added to the organic layer, followed by additon of sodium bicarbonate (saturated in water, 5 mL), and the mixture was well shaken. The mixture was washed with NaOH (1.0 M, 10 mL), water (2 X 10 mL), brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 20% ethyl acetate in hexane to give the title compound (to give the title amine (113 mg, 91%). ¹HNMR (300 MHz, CDCl₃) δ 7.94 (2d'd, 1 H), 7.31-7.18 (m, 4 H), 7.10-7.02 (m, 2 H), 3.62,3.61 (2 s's, 3 H), 3.52 (m, 2 H), 3.00-2.85 (m, 4 H), 2.26,2.18 (2 t's, 2 H), 2.06,2.05 (2 s's, 3 H), 1.80-0.80 (m, 13 H), 0.94,0.91 (2 t's, 3 H). MS(CI/NH₃) m/z: 436 (M+H)⁺.

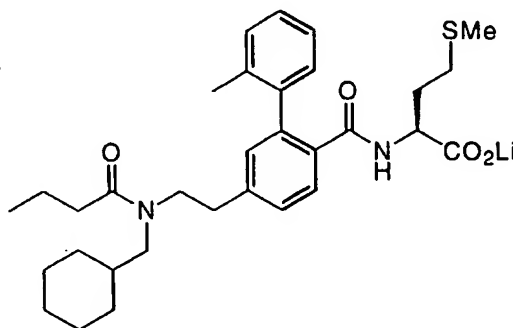


Example 1143C

N-[4-(N-Cyclohexylmethyl-N-butanoylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine

Methyl Ester

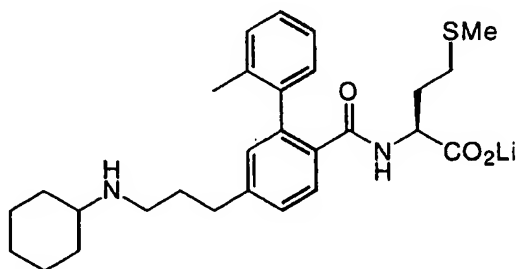
The procedures described in the Example 403E and 403F were used here to convert the above intermediate 1143B (130 mg, 0.300 mmol) to the title methyl ester (112 mg, 66%). ¹H NMR (300 MHz, CDCl₃) δ 7.90 (m, 1 H), 7.35-7.21 (m, 4 H), 7.19 (m, 1 H), 7.03 (br d, 1 H), 5.89 (br d, 1 H), 4.61 (m, 1 H), 3.65 (s, 3 H), 3.52 (m, 2 H), 3.30, 3.07 (2 m's, 2 H), 2.90 (t, 2 H), 2.40-1.97 (m, 10 H), 1.90-1.10 (m, 15 H), 0.92, 0.90 (2 t's, 3 H). MS(Cl/NH₃) m/z: 567 (M+H)⁺.



Example 1143D

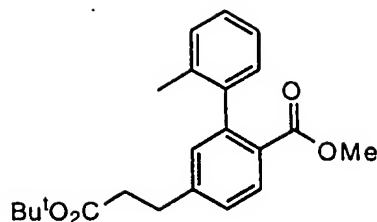
N-[4-(N-Cyclohexylmethyl-N-butanoylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The procedure described in the Example 403I was used here to convert the intermediate 1143C (104 mg) to the title lithium salt (95 mg, 100%). ¹H NMR (300 MHz, dms_o-d₆) δ 7.48 (2 d's, 1 H), 7.31-7.10 (m, 5 H), 7.10-6.87 (m, 2 H), 3.66 (m, 1 H), 3.57-3.39 (m, 2 H), 3.22, 3.09 (2 m's, 2 H), 2.85, 2.79 (2 t's, 2 H), 2.40, 2.25 (2 m's, 2 H), 2.20-1.90 (m, 8 H), 1.83 (m, 1 H), 1.75-1.06 (m, 14 H), 0.87, 0.85 (2 t's, 3 H). MS(ESI-) m/z: 551 (M-H)⁻.



Example 1144

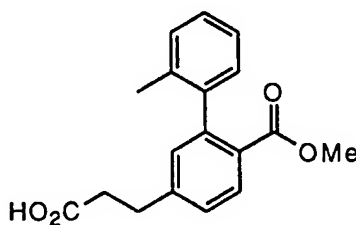
N-[4-(N-Cyclohexylpropyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Example 1144AMethyl 4-(tert-Butoxycarbonyl)ethyl-2-(2-methylphenyl)benzoate

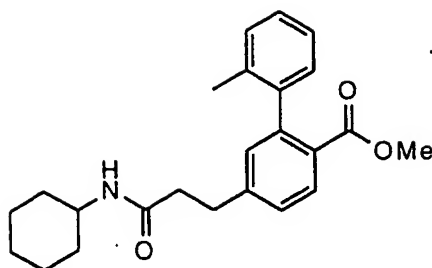
To a solution of (t-butoxycarbonylmethyl)triphenylphosphonium bromide (10.98 g, 24.0 mmol) in THF (150 mL) at 0 °C was added potassium t-butoxide (1.0 M in THF, 24 mL) over 5 min. After 2 h, the aldehyde from example 1171A (20 mmol) in THF (10 mL) was added slowly over 5 min., and the reaction was further stirred for 30 min. The reaction mixture was diluted with hexane (200 mL), and the resulting muddy mixture was filtered through silica gel (200 g), rinsed with ether, and concentrated to give an intermediate olefin.

¹H NMR (300 MHz, CDCl₃) δ 7.97 (d, 1 H), 7.59 (d, 1 H), 7.54 (dd, 1 H), 7.37 (d, 1 H), 7.30-7.27 (m, 3 H), 7.06 (d, 1 H), 6.44 (d, 1 H), 3.61 (s, 3 H), 2.06 (s, 3 H), 1.52 (s, 9 H). MS(CI/NH₃) m/z: 353 (M+H)⁺, 370 (M+NH₄)⁺.

That intermediate was mixed with palladium on carbon (10%, 2.0 g) in ethanol (30 mL), and was stirred under a hydrogen balloon overnight. The mixture was then filtered through CeliteTM (5 g), and the filtrate was concentrated. The residue was then redissolved in ether (100 mL) and the solution was filtered through silica gel (30 g). Concentration of the filtrate afforded the title compound (7.27 g, 99% for 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 7.91 (d, 1H), 7.28-7.15 (m, 4 H), 7.07-7.03 (m, 2 H), 3.60 (s, 3 H), 2.97 (t, 2 H), 2.57 (t, 2 H), 2.05 (s, 3 H), 1.40 (s, 9 H). MS(CI/NH₃) m/z: 355 (M+H)⁺, 372 (M+NH₄)⁺.

Example 1144BMethyl 4-(2-Carboxyethyl)-2-(2-methylphenyl)benzoate

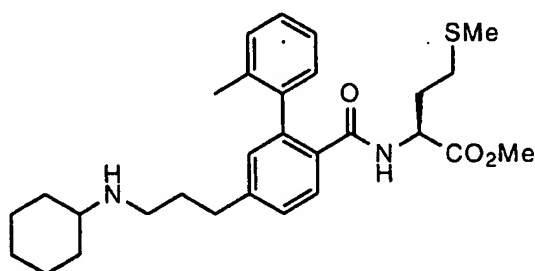
A solution of intermediate 1144A (5.00 g) in trifluoroacetic acid (20 mL) and methyl sulfide (3 mL) was stirred at room temperature for 7 hours. Solvent was then evaporated to give an off-white solid, which was used without further purification.



Example 1144C

12945 Methyl 4-(2-Cyclohexylcarbamoyl)ethyl-2-(2-methylphenyl)benzoate

To a solution of intermediate 1144B (150 mg, 0.50 mmol), oxalyl chloride (2.0 M in DCM, 0.5 mL) in DCM (2 mL) was added a small drop of DMF. After 2 hours at room temperature, the reaction was concentrated to dryness, and redissolved in DCM (3 mL). To it was added cyclohexylamine (99 mg, 1 mmol) and triethylamine (100 mg, 1 mmol). After 15 min., HCl (1.0 M in ether, 2.0 mL) was added to the reaction mixture, and it was filtered through silica gel (5 g). The residue after concentration of the filtrate was purified by column chromatography with 20% ethyl acetate in hexane to give the title compound (152 mg, 80%).
 12950 ¹H NMR (300 MHz, CDCl₃) δ 7.90 (d, 1 H), 7.28-7.15 (m, 4 H), 7.07-7.02 (m, 2 H), 5.16 (m, 1 H), 3.72 (m, 1 H), 3.60 (s, 3H), 3.02 (t, 2 H), 2.45 (t, 2 H), 2.05 (s, 3 H), 1.85 (m, 2 H), 1.70-1.55 (m, 3 H), 1.40-0.95 (m, 6 H). MS(Cl/NH₃) m/z: 380 (M+H)⁺, 397 (M+NH₄)⁺.



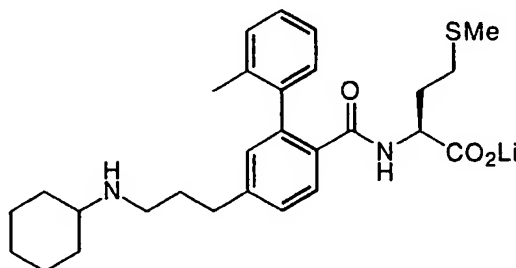
Example 1144D

12960 N-[4-(N-Cyclohexylpropyl)-2-(2-methylphenyl)benzoyl]methionine

A solution of intermediate 1144C (150 mg, 0.40 mmol) and borane (1.0 M in THF, 1.0 mL) in THF (1 mL) was refluxed for 15 hours. Methanol (0.5 mL) was added dropwisely to the reaction, followed by concentrated HCl (0.5 mL), and the mixture was heated at 60 °C for 1 hour. The reaction mixture was cooled to room temperature, and was adjusted to pH about 12-14 with sodium carbonate (2.0 M in water). The reaction mixture was then
 12965 partitioned between ethyl acetate (50 mL) and water (5 mL). The organic layer was washed with water (10 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and

concentrated to give the intermediate amine. The amine was used without further purification. MS(Cl/NH₃) m/z: 366 (M+H)⁺.

12970 The procedures described in the Example 403E and 403F were used here to convert the above intermediate amine to the title methyl ester (58%, 3 steps).

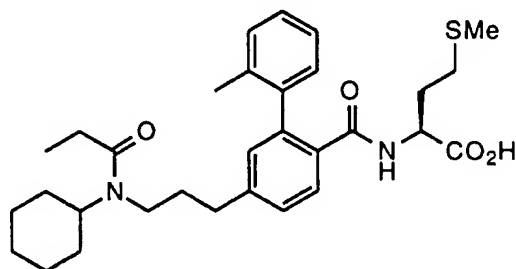


Example 1144E

12975 N-[4-(N-Cyclohexylpropyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The procedure described in the Example 403I was used here to convert the intermediate 1144D (121 mg) to the title lithium salt (107 mg, 100%). ¹H NMR (300 MHz, dms_o-d₆) δ 7.45 (d, 1 H), 7.27-7.08 (m, 4 H), 7.02-6.93 (m, 2 H), 6.90 (m, 1 H), 3.80 (m, 1 H), 3.65 (m, 1 H), 3.30 (m, 2 H), 2.64 (t, 2 H), 2.20-1.80 (m, 10 H), 1.80-1.45 (m, 7 H), 1.30-0.88 (m, 6 H). MS(ESI⁻) m/z: 481 (M-H)⁻.

12980



Example 1145

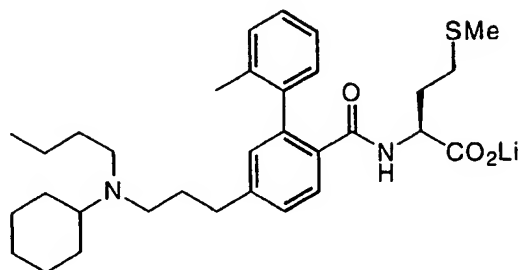
12985 N-[4-(N-Cyclohexyl-N-propanoylaminopropyl)-2-(2-methylphenyl)benzoyl]methionine

To a stirred mixture of 1144E (70 mg, 0.14 mmol) in THF (1 mL) and saturated aqueous sodium bicarbonate (1 mL) was added propionyl chloride (0.10 mL). After 10 min, the reaction mixture was adjusted to pH 4-5, and it was then partitioned between ethyl acetate (50 mL) and water (5 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was heated at 60 °C under high vacuum for 5 hours to give the title compound (59 mg, 78%). ¹H NMR (300 MHz, dms_o-d₆) δ 7.47 (m, 1 H), 7.32-6.97 (m, 7 H), 4.25 (m, 1 H),

12990

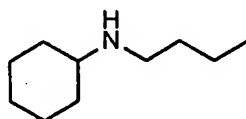
3.57 (m, 1 H), 3.35 (m, 2 H), 2.80-2.60 (m, 2 H), 2.30-1.85 (m, 12 H), 1.85-1.45 (m, 7 H), 1.30-0.88 (m, 9 H). MS(ESI-) m/z: 537 (M-H)⁻.

12995

Example 1146

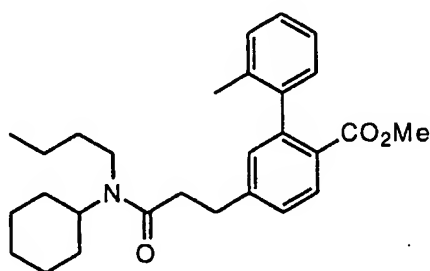
N-[4-(N-Cyclohexyl-N-butylaminopropyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

13000

Example 1146AN-Butylcyclohexylamine

13005

The procedures described in the Example 1178E and 1178F were used here to convert butyric chloride and cyclohexylamine to the title amine in 86% yield. ¹H NMR (300 MHz, CDCl₃) δ 2.62 (t, 2 H), 2.41 (m, 1 H), 1.95-1.00 (m, 15 H), 0.92 (t, 3 H). MS(CI/NH₃) m/z: 156 (M+H)⁺.



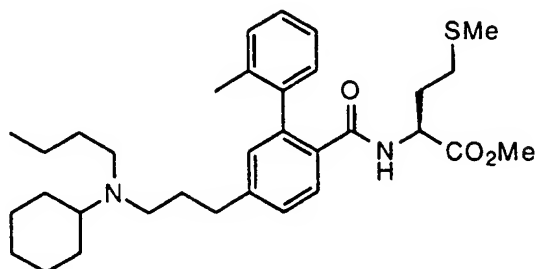
13010

Example 1146BMethyl N-[4-(N-Cyclohexyl-N-butylaminopropyl)-2-(2-methylphenyl)benzoate

The procedure described in the Example 1144C was used here to convert the intermediate 1144B (298 mg) and N-butylcyclohexylamine (intermediate 1146A, 310 mg, 2.0 mmol) to the title methyl ester (233 mg, 54%). ¹H NMR (300 MHz, CDCl₃) δ 7.90 (2 d's, 1 H), 7.30-7.15 (m, 4 H), 7.07 (m, 2 H), 4.25 (m, 1 H), 3.60 (s, 3 H), 3.18 (m, 1

13015

H), 3.05 (m, 3 H), 2.62 (m, 2 H), 2.06 (2s's, 3 H), 1.85-1.05 (m, 14 H), 0.90 (2 t's, 3 H). MS(CI/NH₃) m/z: 436 (M+H)⁺.



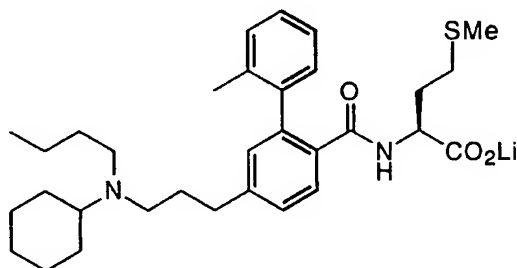
13020

Example 1146C

N-[4-(N-Cyclohexyl-N-butylaminopropyl)-2-(2-methylphenyl)benzoyl]methionine Methyl Ester

The procedure described in the Example 1144C was used here to convert the intermediate 1146B (230 mg) to the title methyl ester (184 mg, 63%). ¹H NMR (300 MHz, CDCl₃) δ 7.90 (2 d's, 1 H), 7.35-7.19 (m, 4 H), 7.03 (m, 1 H), 5.89 (m, 1 H), 4.62 (m, 1 H), 3.66 (s, 3 H), 3.05 (m, 1 H), 2.66 (t, 2 H), 2.46 (t, 2 H), 2.41 (t, 2 H), 2.20-2.00 (4 s's, 6 H), 2.05 (m, 2 H), 1.90-1.00 (m, 18 H), 0.90 (t, 3 H). MS(CI/NH₃) m/z: 553 (M+H)⁺.

13030

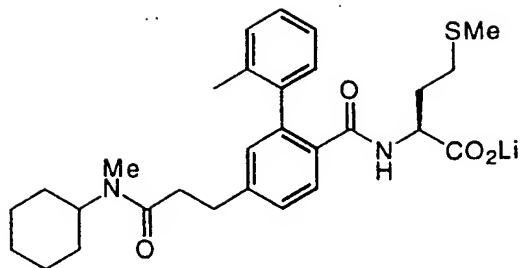


Example 1146D

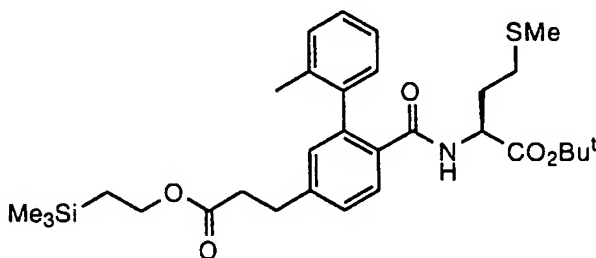
N-[4-(N-Cyclohexyl-N-butylaminopropyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The procedure described in the Example 403I was used here to convert the intermediate 1146C (179 mg) to the title lithium salt (153 mg, 81%). ¹H NMR (300 MHz, dms_o-d₆) δ 7.46 (m, 1 H), 7.35-7.08 (m, 4 H), 7.07-6.90 (m, 2 H), 3.70 (m, 1 H), 3.05 (m, 1 H), 2.64 (t, 2 H), 2.37 (m, 4 H), 2.20-1.90 (m, 8 H), 1.90-0.95 (m, 18 H), 0.85 (t, 3 H). MS(ESI⁻) m/z: 537 (M-H)⁻.

13040

Example 1147

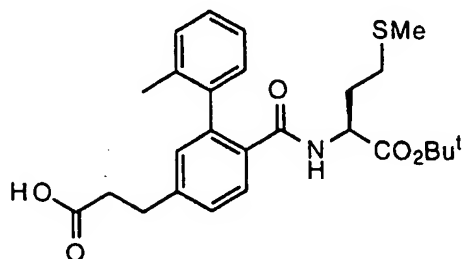
N-[4-(N-Cyclohexyl-N-methylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine
lithium salt

Example 1147A

[4-(2-Trimethylsilylethoxycarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine tert-Butyl
Ester

A solution of intermediate 1144A (875 mg, 2.38 mmol) and LiOH (5.3 M in water, 2.0 mL) in methanol (5 mL) was refluxed 15 hours. The mixture was then acidified with concentrated HCl (1 mL) to pH<3. The reaction mixture was then partitioned between ethyl acetate (100 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The resulting white solid was desolved in DMF (10 mL). To it was added 2-trimethylsilylethanol (0.357 mL, 2.49 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (545 mg, 2.84 mmol), and DMAP (10 mg). After 2 hours, triethylamine (809 mg, 8.0 mmol) L-methionine tert-butyl ester hydrochloride (725 mg, 3.0 mmol), 1-hydroxybenzotriazole (400 mg, 3.0 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (577 mg, 3.0 mmol). After 15 hours at room temperature, the reaction mixture was partitioned between ethyl acetate (100 mL) and water (10 mL). The organic layer was washed with water (3 X 15 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 10% ethyl acetate in hexane to give the title compound (859 mg, 68%). ¹H NMR (300 MHz, CDCl₃) δ 7.83 (2 d'd, 1 H), 7.33-7.15 (m, 5 H), 7.04 (br s, 1 H), 5.85 (br d, 1 H), 4.50 (m, 1 H), 4.16 (t, 2 H), 3.00 (t, 2 H), 2.63 (t, 2 H),

2.17, 2.07, 2.03, 2.02 (4 s's, 6 H), 2.00 (m, 2 H), 1.80 (m, 1 H), 1.55 (m, 1 H), 1.40 (s, 9 H), 0.95 (t, 2 H), 0.03 (s, 9 H). MS(CI/NH₃) m/z: 572 (M+H)⁺.



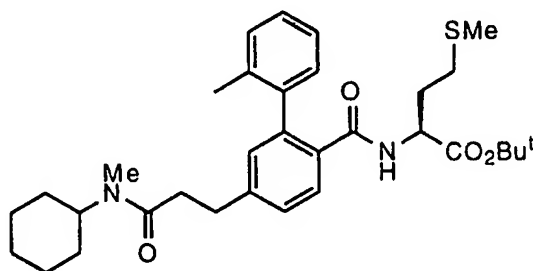
13070

Example 1147B

[4-(2-Carboxyethyl)-2-(2-methylphenyl)benzoyl]methionine tert-Butyl Ester

A solution of intermediate 1147A (841 mg, 1.57 mmol), tetrabutylammomium fluoride (820 mg, 3.14 mmol) in DMF (5 mL) was stirred overnight. The reaction mixture was then adjusted to pH 3-5, and was partitioned between ethyl acetate (100 mL) and water (20 mL). The organic layer was washed with water (2 X 20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to give the title compound. The crude product was used without further purification. ¹H NMR (300 MHz, CDCl₃) δ 7.83 (2 d'd, 1 H), 7.33-7.15 (m, 5 H), 7.05 (br s, 1 H), 5.87 (m, 1 H), 4.50 (m, 1 H), 3.01 (t, 2 H), 2.71 (t, 2 H), 2.20-2.02 (4 s's, 6 H), 2.00 (m, 2 H), 1.80 (m, 1 H), 1.59 (m, 1 H), 1.40 (s, 9 H). MS(CI/NH₃) m/z: 472 (M+H)⁺.

13080



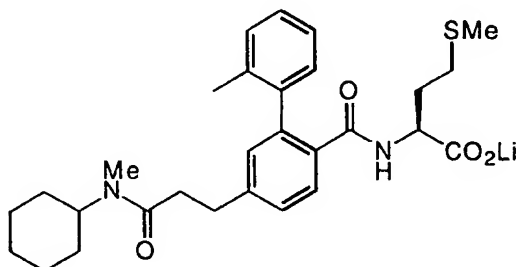
Example 1147C

N-[4-(N-Cyclohexyl)-N-methylaminocarbonyl]ethyl-2-(2-methylphenyl)benzoyl]methionine tert-Butyl Ester

A solution of intermediate 1147B (50 mg, 0.115 mmol), triethylamine (100 mg), 1-hydroxybenzotriazole (31 mg, 0.23 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (44 mg, 0.23 mmol), and N-methylcyclohexylamine (26 mg, 0.23 mmol) in DMF (2 mL) was stirred 15 hours at room temperature. The reaction mixture was then partitioned between ethyl acetate (50 mL) and water (5 mL). The organic layer was washed with water (3 X 5 mL), brine (5 mL), dried over anhydrous magnesium sulfate, filtered and

13090

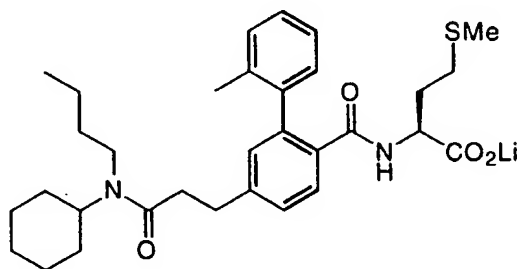
concentrated. The residue was purified by column chromatography with 40% ethyl acetate in hexane to give the title compound (44 mg, 68%). ¹H NMR (300 MHz, CDCl₃) δ 7.84 (m, 1 H), 7.33-7.15 (m, 5 H), 7.05 (br s, 1 H), 5.84 (m, 1 H), 4.47 (m, 2 H), 3.02 (t, 2 H), 2.81, 2.77 (2s's, 3 H), 2.62 (m, 2 H), 2.20-1.97 (m, 8 H), 1.90-1.25 (m, 12 H), 1.40 (s, 9 H). MS(CI/NH₃) m/z: 567 (M+H)⁺.



Example 1147D

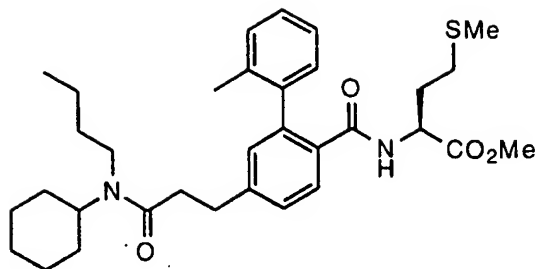
N-[4-(N-Cyclohexyl-N-methylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

The intermediate 1147C (40 mg) was stirred with HCl (4.0 N in dioxane, 1.0 mL) in DCM (1 mL) at room temperature for 15 hours. Solvent was then evaporated, and the residue was desolved in acetonitrile (1 mL), treated with 1.1 equivalent of LiOH (1.0 M in water, 0.078 mL), and freeze-dried to give the title compound (37 mg, 100%). ¹H NMR (300 MHz, dmso-d₆) δ 7.44 (d, 1 H), 7.30 (m, 1 H), 7.25-7.08 (m, 4 H), 7.03 (m, 1 H), 6.87 (m, 1 H), 4.23 (m, 1 H), 3.66 (m, 1 H), 2.87 (m, 2 H), 2.74, 2.66 (2s's, 3 H), 2.62 (m, 2 H), 2.20-1.90 (m, 8 H), 1.90-1.25 (m, 12 H). MS(ESI-) m/z: 509 (M-H)⁻.



Example 1148

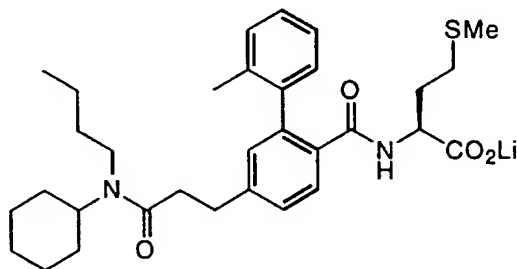
N-[4-(N-Cyclohexyl-N-butylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

Example 1148A

N-[4-(N-Cyclohexyl-N-butylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine

Methyl ester

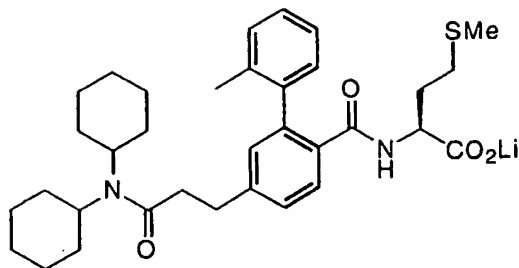
The procedures described in the Example 403E and 403F were used here to convert the intermediate 1146B (102mg) to the title methyl ester (117 mg, 90%). ¹HNMR (300 MHz, CDCl₃) δ 7.91 (2 d's, 1 H), 7.35-7.15 (m, 5 H), 7.06 (br s, 1 H), 6.88 (m, 1 H), 4.61 (m, 1 H), 3.49 (m, 1 H), 3.66 (s, 3 H), 3.20-3.00 (m, 4 H), 2.66-2.50 (m, 2 H), 2.20-2.00 (m, 8 H), 1.90-0.95 (m, 16 H), 0.91 (t, 3 H). MS(Cl/NH₃) m/z: 566 (M+H)⁺.

Example 1148B

N-[4-(N-Cyclohexyl-N-butylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine

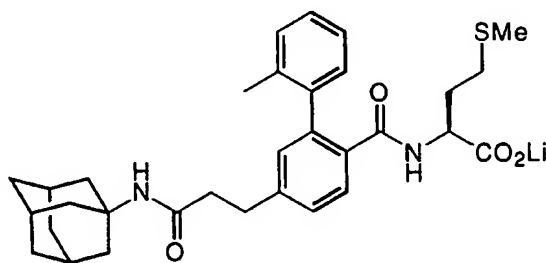
lithium salt

The procedure described in the Example 403I was used here to convert the intermediate 1148A (108 mg) to the title lithium salt (91 mg, 83%). ¹HNMR (300 MHz, dmso-d₆) δ 7.44 (d, 1 H), 7.27 (t, 1 H), 7.23-7.05 (m, 3 H), 7.04-6.91 (m, 2 H), 6.89 (d, 1 H), 4.07 (m, 1 H), 3.65 (m, 1 H), 3.06 (m, 2 H), 2.88 (m, 2 H), 2.65, 2.57 (2 t't, 2 H), 2.20-1.90 (m, 8 H), 1.90-0.95 (m, 16 H), 0.84 (t, 3 H). MS(ESI-) m/z: 537 (M-H)⁻.

Example 1149

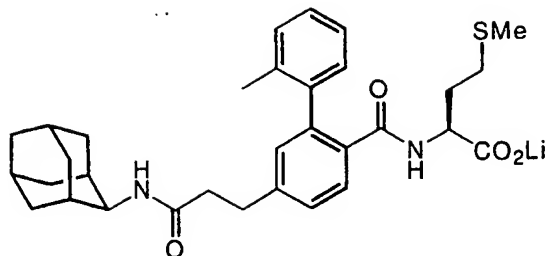
13140 N-[4-(N,N-dicyclohexylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium
salt

The procedures described in the Example 1147C and 1147D were used here to convert 1147B (50 mg) to the title lithium salt (30 mg, 45%, 2 steps). ¹HNMR (300 MHz, dms_o-d₆) δ 7.44 (d, 1 H), 7.30 (m, 1 H), 7.25-7.08 (m, 4 H), 7.03 (m, 1 H), 6.87 (m, 1 H), 4.18 (m, 1 H), 3.66 (m, 1 H), 2.87 (t, 2 H), 2.60 (t, 2 H), 2.20-1.90 (m, 8 H), 1.75-1.00 (m, 22 H). MS(ESI⁻) m/z: 577 (M-H)⁻.

Example 1150

13150 N-[4-(N-adamant-1-ylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium
salt

The procedures described in the Example 1147C and 1147D were used here to convert 1147B (50 mg) to the title lithium salt (40 mg, 62%, 2 steps). ¹HNMR (300 MHz, dms_o-d₆) δ 7.63 (d, 1 H), 7.44 (d, 1 H), 7.27-7.05 (m, 5 H), 6.98 (m, 1 H), 6.88 (m, 1 H), 3.80 (m, 1 H), 3.64 (m, 1 H), 2.87 (m, 2 H), 2.50 (m, 2 H), 2.20-1.80 (m, 17 H), 1.77-1.45 (m, 8 H). MS(ESI⁻) m/z: 547 (M-H)⁻.



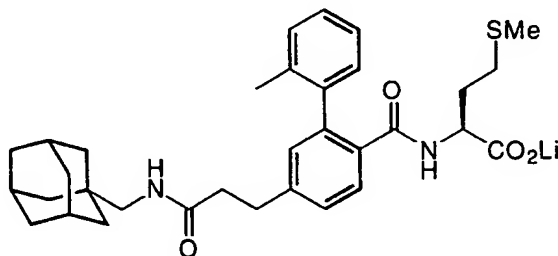
13160

Example 1151

N-[4-(N-adamant-2-ylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

The procedures described in the Example 1147C and 1147D were used here to convert 1147B (50 mg) to the title lithium salt (41 mg, 64%, 2 steps). ¹HNMR (300 MHz, dmso-d₆) δ 7.44 (m, 1 H), 7.30-7.05 (m, 6 H), 7.00 (m, 1 H), 6.88 (m, 1 H), 3.67 (m, 1 H), 2.82 (m, 2 H), 2.35 (m, 2 H), 2.20 -1.45 (m, 25 H). MS(ESI-) m/z: 547 (M-H)⁻.

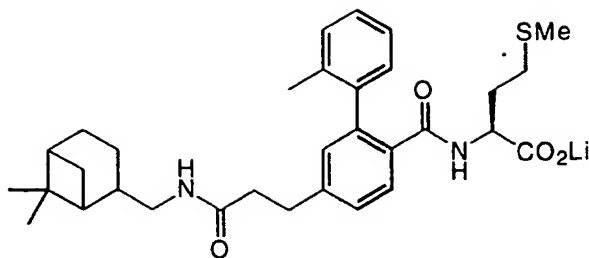
13170

Example 1154

N-[4-(N-adamant-1-ylmethylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

The procedures described in the Example 1147C and 1147D were used here to convert 1147B (50 mg) to the title lithium salt (47 mg, 72%, 2 steps). ¹HNMR (300 MHz, dmso-d₆) δ 7.61 (t, 1 H), 7.44 (d, 1 H), 7.25 (dd, 1 H), 7.24-7.08 (m, 4 H), 6.99 (br s, 1 H), 6.88 (m, 1 H), 3.62 (m, 1 H), 2.82 (t, 2 H), 2.73 (d, 2 H), 2.45 (t, 2 H), 2.20-1.90 (m, 8 H), 1.75-1.48 (m, 11 H), 1.35 (d, 6 H). MS(ESI-) m/z: 561 (M-H)⁻.

13180

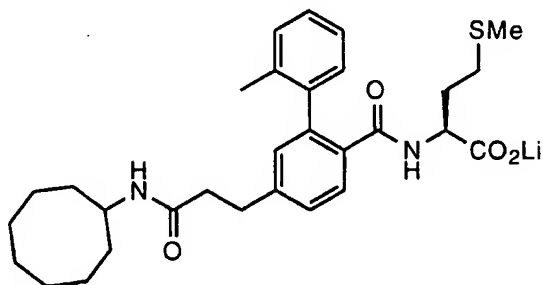
**Example 1155**

N-[4-(N-Mytanylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

13185

The procedures described in the Example 1147C and 1147D were used here to convert 1147B (50 mg) to the title lithium salt (45 mg, 70%, 2 steps). ¹H NMR (300 MHz, dmso-d₆) δ 7.60 (t, 1 H), 7.44 (d, 1 H), 7.28-7.08 (m, 5 H), 6.99 (br s, 1 H), 6.88 (m, 1 H), 3.66 (m, 1 H), 3.00 (m, 2 H), 2.83 (t, 2 H), 2.39 (t, 2 H), 2.33-1.20 (m, 19 H), 1.13 (s, 3 H), 0.97 (s, 3 H). MS(ESI-) m/z: 549 (M-H)⁻.

13190

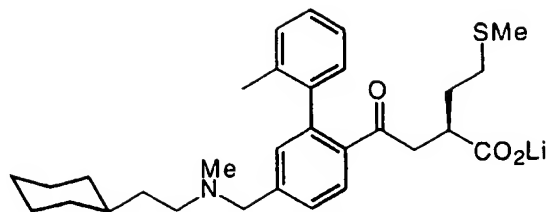
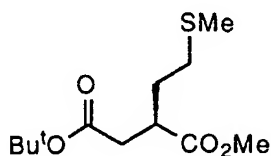
**Example 1157**

N-[4-(N-Cyclooctanylaminocarbonyl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

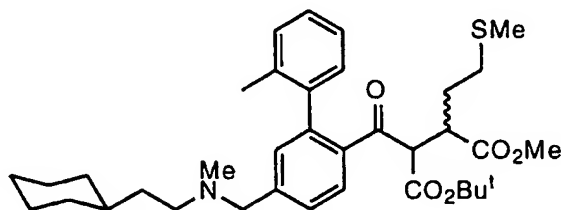
13195

The procedures described in the Example 1147C and 1147D were used here to convert 1147B (50 mg) to the title lithium salt (31 mg, 51%, 2 steps). ¹HNMR (300 MHz, dmso-d₆) δ 7.67 (d, 1 H), 7.44 (d, 1 H), 7.25-7.08 (m, 5 H), 6.96 (br s, 1 H), 6.88 (m, 1 H), 3.72 (m, 1 H), 3.63 (m, 1 H), 2.85 (t, 2 H), 2.36 (t, 2 H), 2.20-1.90 (m, 8 H), 1.90-1.30 (m, 16 H). MS(ESI-) m/z: 523 (M-H)⁻.

13200

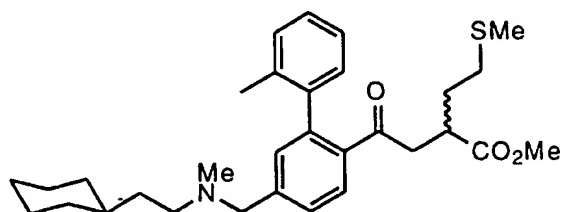
Example 1158Example 1158AMethyl 2-(tert-butoxycarbonylmethyl)-4-methylthiobutyrate

To a -78 °C solution of methyl 4-methylthiobutyrate (1.48 g, 10.0 mmol) in THF (20 mL) was added sodium bis(trimethylsilyl)amide (1.0 M in THF, 11 mL). After 30 min, tert-butyl bromoacetate (2.34 g, 12.0 mmol) was added to the reaction, and the reaction mixture was gradually warmed to the room temperature over 6 hours. The reaction mixture was then partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with water (2 X 20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 5% ethyl acetate in hexane to give the title compound (1.21 g, 46%). ¹HNMR (300 MHz, CDCl₃) δ 3.75 (s, 3 H), 2.71 (t, 2 H), 2.51 (t, 2 H), 2.32 (m, 1 H), 2.06 (s, 1 H), 1.89 (t, 1 H), 1.41 (s, 9 H). MS(Cl/NH₃) m/z: 263 (M+H)⁺.

Example 1158B

To a solution of the acid from example 608C (530 mg, 1.32 mmol) in DCM (2 mL) was added oxalyl chloride (2.0 M in DCM, 1.5 mL), followed by a small drop of DMF. After 2 hours at room temperature, the solvent was removed, and the residue was further dried under high vacuum (1 mmHg) for 1 hour. The solid (acid chloride) was redissolved in THF (5 mL).

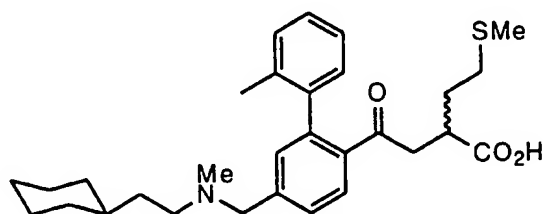
To a -78°C solution of 1158A (1.21 g, 4.61 mmol) in THF (10 mL) in a separate flask was added sodium bis(trimethylsilyl)amide (1.0 M in THF, 5.28 mL). After 30 min., the acid chloride solution was added slowly to the reaction mixture via a cannula. After 1 hour, the reaction mixture was quenched with saturated aqueous ammonium chloride (3 mL) at -78°C . After it reached the room temperature, the reaction mixture was then partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with sodium bicarbonate (saturated in water, 10 mL), water (2 X 10 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 30% ethyl acetate in hexane to give the title compound (430 mg, 53%). ^1H NMR is messy because of 4 diastereomers exist. MS(CI/ NH_3) m/z: 610 (M+H) $^+$.



Example 1158C

Methyl 3-[4-(N-cyclohexyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoylmethyl]-4-methylthiobutyrate

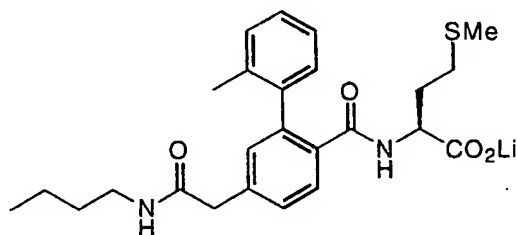
A solution of 1158B (420 mg, 0.69 mmol) in HCl (4.0 M in 1,4-dioxane, 5 mL) was heated at 80°C for 2 hours. Solvent was evaporated, and the residue was redissolved in ethyl acetate (100 mL). The mixture was then washed with sodium bicarbonate (saturated in water, 20 mL), water (20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 30% ethyl acetate in hexane to give the title compound (121 mg, 34%). ^1H NMR (300 MHz, CDCl_3) δ 7.62 (d, 1 H), 7.40 (br d, 1 H), 7.31-7.12 (m, 4 H), 7.07 (br d, 1 H), 3.62 (s, 3 H), 3.54 (br s, 2 H), 2.85 (m, 1 H), 2.71 (m, 1 H), 2.40 (m, 2 H), 2.35-2.00 (m, 12 H), 1.80-0.80 (m, 15 H). MS(CI/ NH_3) m/z: 510 (M+H) $^+$.



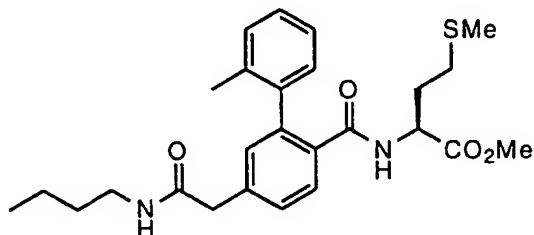
Example 1158D

3-[4-(N-Cyclohexyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoylmethyl]-4-methylthiobutyric acid

The intermediate 1158C (112 mg) in MeOH (2 mL) and lithium hydroxide (1.0 M in water, 0.7 mL) was heated at 50 °C for 5 hours. The reaction mixture was then adjusted to pH 4-5 with KH_2PO_4 (saturated in water), and extracted with ethyl acetate (3 X 20 mL). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give the title compound (110 mg, 100%). ^1H NMR (300 MHz, $\text{dms}\text{-d}_6$) δ 7.77 (m, 1 H), 7.61 (br d, 1 H), 7.40 (m, 1 H), 7.35-7.15 (m, 3 H), 7.07 (m, 1 H), 4.15 (br loop, 2 H), 2.88 (m, 2 H), 2.69 (m, 1 H), 2.28 (m, 2 H), 2.22-1.96 (m, 11 H), 1.72-0.80 (m, 15 H). MS(ESI-) m/z : 494 (M-H) $^-$.



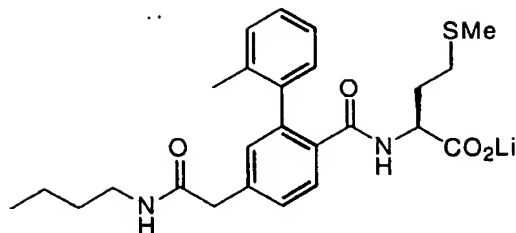
Example 1159



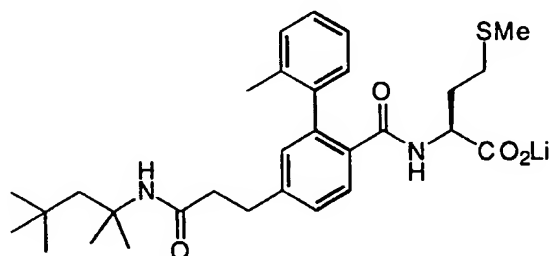
Example 1159A

N-[4-(N-butylaminocarbonylmethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

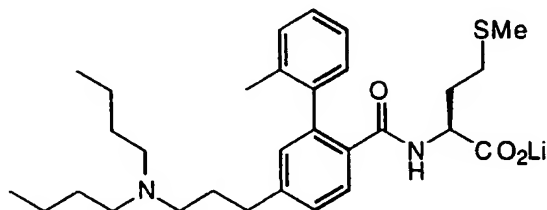
The procedures described in the Example 403E and 403F were used here to convert intermediate 1142A (61 mg, 0.18 mmol) to the title methyl ester (70 mg, 83%). ^1H NMR (300 MHz, CDCl_3) δ 7.95 (2 d's, 1 H), 7.39-7.15 (m, 5 H), 7.12 (br s, 1 H), 5.91 (br d, 1 H), 5.35 (m, 1 H), 4.63 (m, 1 H), 3.67 (s, 3 H), 3.61 (s, 2 H), 3.24 (q, 1 H), 2.20-1.99 (m, 8 H), 1.85 (m, 1 H), 1.60 (m, 1 H), 1.42 (m, 2 H), 1.27 (m, 2 H), 0.88 (t, 3 H). MS(CI/ NH_3) m/z : 471 (M+H) $^+$.

**Example 1159B****N-[4-(N-butylaminocarbonylmethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The procedure described in the Example 403I was used here to convert the intermediate 1159A (63 mg) to the title lithium salt (62 mg, 100%). ¹H NMR (300 MHz, dmso-d₆) δ 8.10 (t, 1 H), 7.57 (d, 1 H), 7.40 (br d, 1 H), 7.37-7.20 (m, 4 H), 7.17 (br s, 1 H), 7.04 (br d, 1 H), 3.75 (m, 1 H), 3.54 (s, 2 H), 3.13 (q, 2 H), 2.28-1.85 (m, 8 H), 1.78 (m, 1 H), 1.64 (m, 1 H), 1.47 (m, 2 H), 1.35 (m, 2 H), 0.93 (t, 3 H). MS(ESI-) m/z: 455 (M-H)⁻.

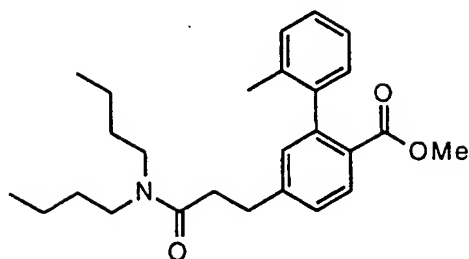
**Example 1160****N-[4-(N-(2,2,4,4-tetramethylbutylamino)carbonylethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The procedures described in the Example 1147C and 1147D were used here to convert 1147B (50 mg) to the title lithium salt (50 mg, 81%, 2 steps). ¹H NMR (300 MHz, dmso-d₆) δ 7.44 (d, 1 H), 7.26 (br s, 1 H), 7.25-7.08 (m, 5 H), 6.98 (br s, 1 H), 6.88 (m, 1 H), 3.63 (m, 1 H), 2.82 (t, 2 H), 2.32 (t, 2 H), 2.20-1.90 (m, 8 H), 1.75-1.50 (m, 2 H), 1.67 (s, 2 H), 1.23 (s, 6 H), 0.89 (s, 9 H). MS(ESI-) m/z: 525 (M-H)⁻.



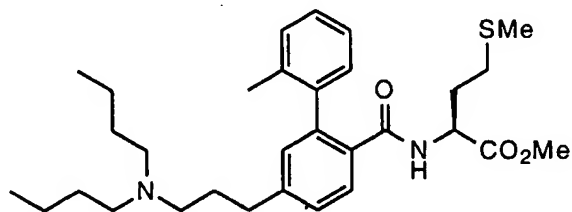
Example 1161

13305

Example 1161AMethyl 4-(N,N-Dibutylaminocarbonyl)ethyl-2-(2-methylphenyl)benzoate

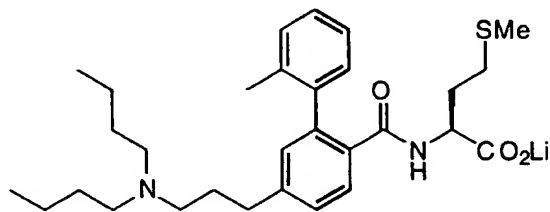
13310 The procedure described in the Example 1144C was used here to convert the intermediate 1144B (150 mg, 0.5 mmol) and dibutylamine (129 mg, 1 mmol) to the title methyl ester (203 mg, 99%). ^1H NMR (300 MHz, CDCl_3) δ 7.90 (d, 1 H), 7.29-7.16 (m, 4 H), 7.06 (m, 2 H), 3.60 (s, 3 H), 3.30 (dt, 2 H), 3.14 (t, 2 H), 3.05 (t, 2 H), 2.61 (t, 2 H), 2.05 (s, 3 H), 1.46 (m, 2 H), 1.27 (m, 2 H), 0.90 (t, 6 H). MS(Cl/NH_3) m/z : 410 ($\text{M}+\text{H}$) $^+$.

13315

Example 1161BN-[4-(N,N-Dibutylaminopropyl)-2-(2-methylphenyl)benzoyl]methionine Methyl Ester

13320 The procedures described in the Example 403E and 403F were used here to convert the above intermediate 1161A (195 mg, 0.48 mmol) to the title methyl ester (165 mg, 66%). ^1H NMR (300 MHz, CDCl_3) δ 7.90 (2 d'd, 1 H), 7.35-7.19 (m, 5 H), 7.02 (br s, 1 H), 5.88 (br d, 1 H), 4.61 (m, 1 H), 3.65 (s, 3 H), 2.66 (t, 2 H), 2.40 (m, 6 H), 2.20-2.00 (m, 8 H), 1.90-1.70 (m, 3 H), 1.59 (m, 1 H), 1.45-1.20 (m, 8 H), 0.89 (t, 6 H). MS(Cl/NH_3) m/z : 520 ($\text{M}+\text{H}$) $^+$.

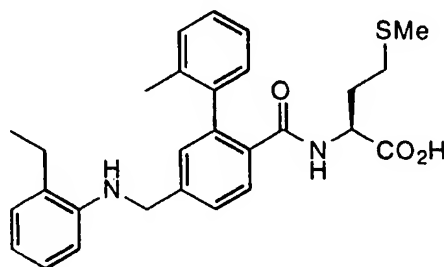
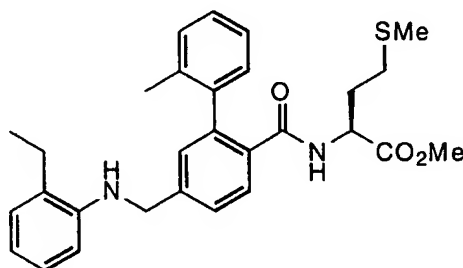
13325



Example 1161CN-[4-(N,N-Dibutylaminopropyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

13330 The procedure described in the Example 403I was used here to convert the intermediate 1161B (156 mg) to the title lithium salt (151 mg, 98%). ¹H NMR (300 MHz, dms_o-d₆) δ 7.46 (d, 1 H), 7.34-7.08 (m, 5 H), 6.97 (m, 2 H), 3.75 (m, 1 H), 2.63 (t, 2 H), 2.32 (m, 6 H), 2.20-1.80 (m, 9 H), 1.70 (m, 3 H), 1.60 (m, 1 H), 1.38-1.20 (m, 8 H), 0.84 (t, 6 H). MS(ESI-) m/z: 511 (M-H)⁻.

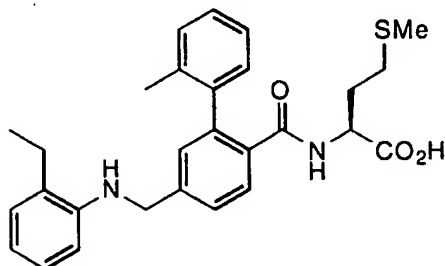
13335

Example 1164

13340

Example 1164AN-[4-N-(2-Ethylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

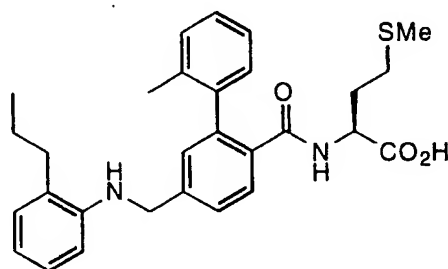
The desired ester was prepared using the method described in Example 403H starting with the compound described in Example 403G and 2-ethylaniline. m/e (ESI) 489 (MH⁺)



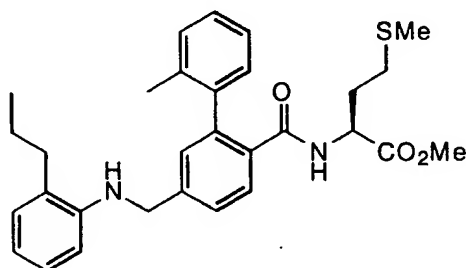
13345

Example 1164BN-[4-N-(2-Ethylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I starting with compound prepared in Example 1164A. ^1H (300MHz, CDCl_3 , δ) 7.96 (1H, t, J=9Hz), 7.48 (1H, bd, J=8Hz), 7.20-7.00 (8H, m), 6.77 (1H, t, J=9Hz), 6.57 (1H, bd, J=8Hz), 5.89 (1H, bd, J=8Hz), 4.58 (1H, m), 4.46 (2H, s), 2.55 (2H, q, J=8Hz), 2.20-2.00 (8H, m), 1.90 (1H, m), 1.57 (1H, m), 1.25 (3H, t, J=8Hz). m/e (ESI) 475 (MH^+)
 Anal.calc. for $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_3\text{S} \cdot 0.25 \text{H}_2\text{O}$ C 69.90, H 6.81, N 5.82 Found C 69.64, H 6.66, N 5.65



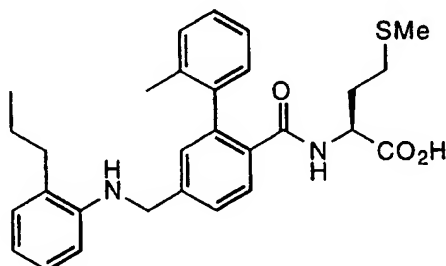
Example 1165



Example 1165A

N-[4-N-(2-Propylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

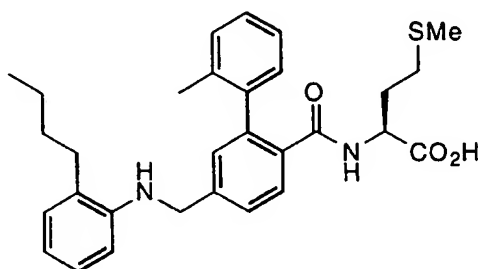
The desired ester was prepared using the method described in Example 403H starting with the compound described in Example 403G and 2-propylaniline. m/e (ESI) 503 (MH^+)



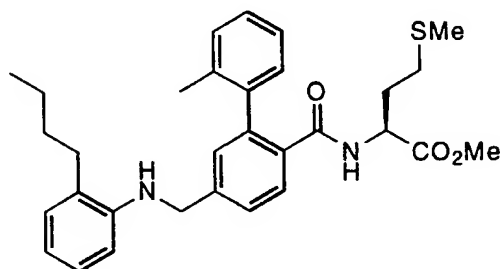
Example 1165B

N-[4-N-(2-Propylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I starting with compound prepared in Example 1165A. ¹H (300MHz, CDCl₃, δ) 7.98 (1H, t, J=9Hz), 7.47 (1H, dd, J=8&2Hz), 7.40-7.10 (6H, m), 7.03 (2H, m), 6.72 (1H, t, J=9Hz), 6.57 (1H, m), 5.86 (1H, bd, J=8Hz), 4.58 (1H, m), 4.44 (2H, s), 2.48 (2H, t, J=8Hz), 2.20-2.00 (8H, m), 1.91 (1H, m), 1.65 (2H, q, J=8Hz), 1.57 (1H, m), 1.01 (3H, t, J=8Hz). m/e (ESI) 489 (MH⁺) Anal.calc. for C₂₉H₃₄N₂O₃S·0.25 H₂O C 70.34, H 7.02, N 5.66 Found C 70.33, H 6.88, N 5.44

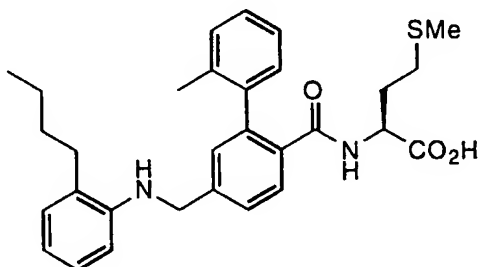
Example 1166

13380

Example 1166A

N-[4-N-(2-Butylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

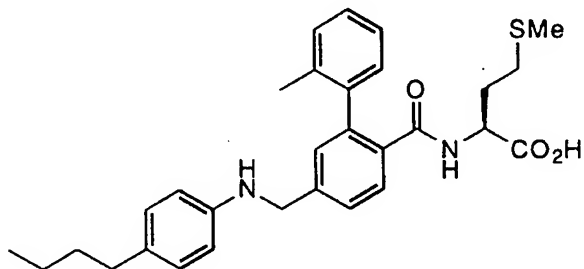
The desired ester was prepared using the method described in Example 403H starting with the compound described in Example 403G and 2-butylaniline. m/e (ESI) 517 (MH⁺)

Example 1166B

N-[4-N-(2-Butylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

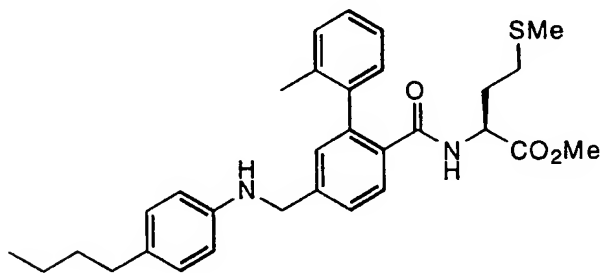
13390 The desired compound was prepared according to the method of Example 403I starting with compound prepared in Example 1166A. ^1H (300MHz, CDCl_3 , δ) 7.97 (1H, t, $J=9\text{Hz}$), 7.45 (1H, bd, $J=8$), 7.40-7.10 (6H, m), 6.98 (2H, d, $J=8\text{Hz}$), 6.73 (1H, t, $J=9\text{Hz}$), 6.57 (1H, m), 5.87 (1H, bd, $J=8\text{Hz}$), 4.58 (1H, m), 4.45 (2H, s), 2.50 (2H, t, $J=8\text{Hz}$), 2.20-2.00 (8H, m), 1.91 (1H, m), 1.70-1.50 (3H, m), 1.40 (2H, q, $J=8\text{Hz}$), 0.93 (3H, t, $J=8\text{Hz}$). m/e (ESI) 503 (MH^+) Anal. calc. for $\text{C}_{30}\text{H}_{36}\text{N}_2\text{O}_3\text{S}\cdot 0.50\text{H}_2\text{O}$ C 70.14, H 7.26, N 5.45 Found C 70.39, H 7.08, N 5.24

13395



Example 1167

13400

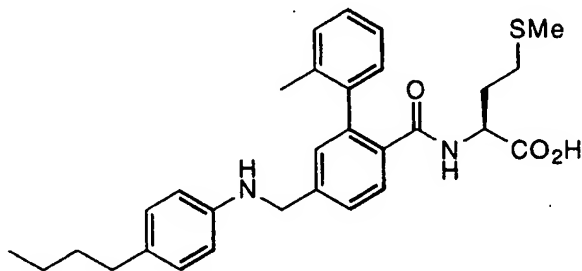


Example 1167A

N-[4-N-(4-Butylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired ester was prepared using the method described in Example 403H starting with the compound described in Example 403G and 4-butylaniline. m/e (ESI) 517 (MH^+)

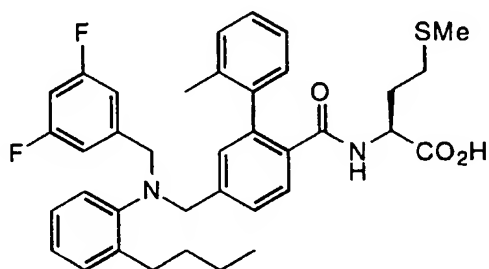
13405



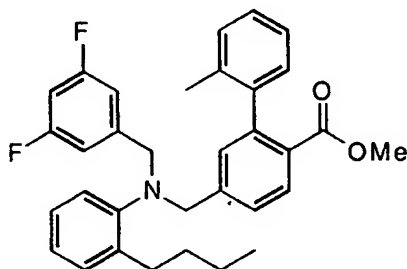
Example 1167B

N-[4-N-(4-Butylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

13410 The desired compound was prepared according to the method of Example 403I
 starting with compound prepared in Example 1167A. ^1H (300MHz, CDCl_3 , δ) 7.98 (1H, t, $J=9\text{Hz}$), 7.47 (1H, bd, $J=8$), 7.40-7.10 (6H, m), 7.04 (2H, d, $J=9\text{Hz}$), 6.56 (2H, d, $J=9\text{Hz}$), 5.88 (1H, bd, $J=8\text{Hz}$), 4.57 (1H, m), 4.40 (2H, s), 2.48 (2H, t, $J=8\text{Hz}$), 2.20-
 13415 2.00 (8H, m), 1.90 (1H, m), 1.53 (3H, m), 1.32 (2H, m), 0.92 (3H, t, $J=8\text{Hz}$). m/e (ESI) 503 (MH^+) Anal. calc. for $\text{C}_{30}\text{H}_{36}\text{N}_2\text{O}_3\text{S}\cdot 0.25\text{H}_2\text{O}$ C 70.76, H 7.23, N 5.50
 Found C 70.77, H 7.07, N 5.35



13420

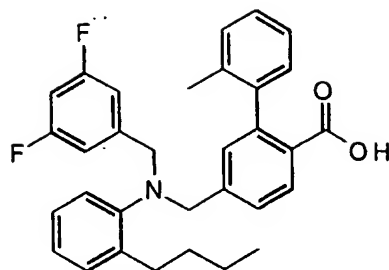
Example 1168Example 1168A

4-N-(2-Butylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methylphenyl)benzoic acid
methyl ester

13425

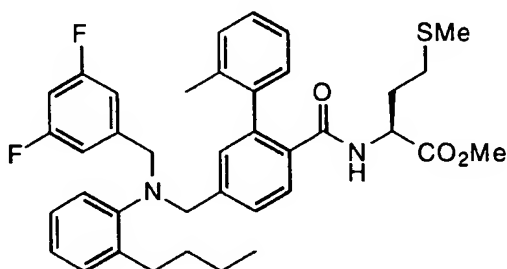
The desired compound was prepared using the method described in Example 1169A
 starting with 2-butylaniline, 3,5-difluorobenzylbromide, and 4-bromomethyl-2-(2-
 methylphenyl)benzoic acid methyl ester, prepared as in Example 1178A-D. m/e (ESI) 514
 (MH $^+$)

13430

Example 1168B

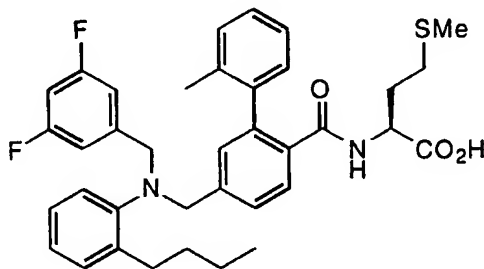
4-N-(2-Butylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methylphenyl)benzoic acid

The desired acid was prepared using the method described in Example 403E starting with the product from Example 1168A.

Example 1168C

N-[4-N-(2-Butylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired compound was prepared using the method described in Example 403F starting with the product from Example 1168B. m/e (ESI) 645 (MH⁺)

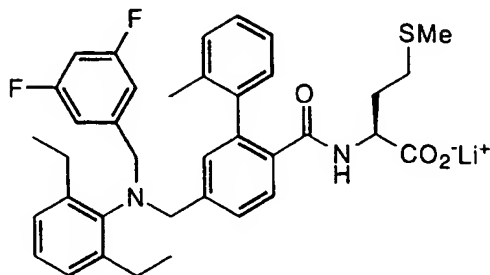
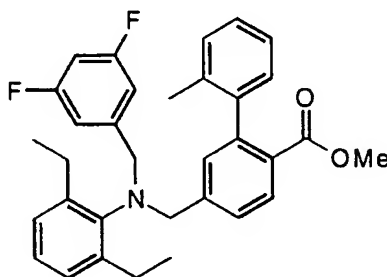
Example 1168D

N-[4-N-(2-Butylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1168C. ¹H (300MHz, CDCl₃, δ) 7.92 (1H, m), 7.40-6.90 (10H, m), 6.81 (2H, bd, J=8Hz), 6.66 (1H, m), 5.84 (1H, m), 4.55 (1H, m), 4.12 (2H, s), 4.04 (2H, s), 2.72 (2H, bt, J=9Hz), 2.20-1.80 (9H, m), 1.52 (3H, m), 1.36

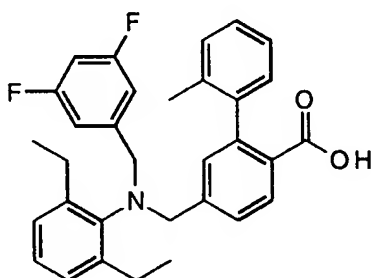
(2H, m), 0.87 (3H, t, J=8Hz). m/e (ESI) 629 (MH⁺) Anal.calc. for C₃₇H₄₀F₂N₂O₃S C 70.45, H 6.39, N 4.40 Found C 70.10, H 6.27, N 4.35

13455

Example 1169Example 1169A

4-N-(2,6-Diethylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methylphenyl)benzoic acid methyl ester

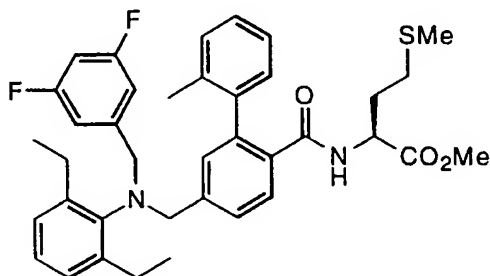
4-Bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester (100 mg, 0.31 mmol), prepared as in Example 1178A-D, 2,6-diethylaniline (0.062 mL, 0.38 mmol), and diisopropylethylamine (0.084 mL, 0.470 mmol) were dissolved in DMF (5 mL), and solution stirred overnight at room temperature. To this mixture was then added diisopropylethylamine (0.084 mL, 0.470 mmol) and α -bromo-3,5-difluorotoluene (0.100 mL, 0.760 mmol), and reaction heated at 80°C for 3 days. Solvents concentrated in vacuo, and residue purified by flash chromatography on silica gel eluting with 2% EtOAc/Hexanes to afford the desired compound as a yellow oil (72 mg, 45%). m/e (ESI) 514 (MH⁺)



Example 1169B4-N-(2,6-Diethylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methylphenyl)benzoic acid

13475

The desired acid was prepared using the method described in Example 403E starting with the product from Example 1169A.

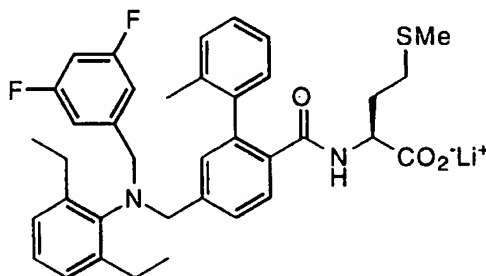


13480

Example 1169CN-[4-N-(2,6-Diethylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired compound was prepared using the method described in Example 403F starting with the product from Example 1169B. m/e (ESI) 645 (MH⁺)

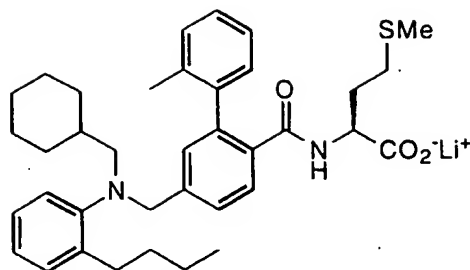
13485

Example 1169DN-[4-N-(2,6-Diethylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

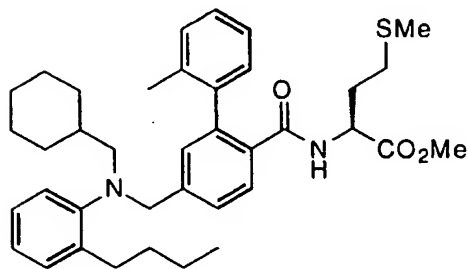
13490

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1169C. ¹H (300MHz, DMSO, δ) 7.43 (1H, d, J=9Hz), 7.30-7.00 (9H, m), 6.85 (4H, m), 4.21 (2H, s), 4.18 (2H, s), 3.65 (1H, m), 2.60-2.40 (4H, m), 2.10-1.50 (10H, m), 1.03 (6H, t, J=8Hz). m/e (ESI) 629 (MH⁻)
Anal.calc. for C₃₇H₃₉F₂LiN₂O₃S·1.50 H₂O C 66.95, H 6.38, N 4.22 Found C 66.79, H

13495 6.34, N 3.93

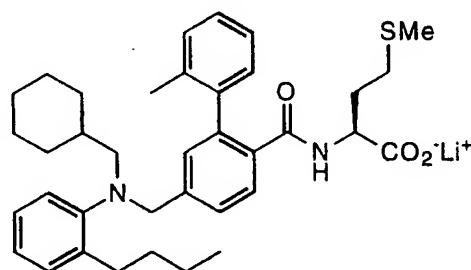
Example 1170

13500

Example 1170A

N-[4-N-(2-Butylphenyl)-N-(cyclohexylmethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

13505 The desired ester was prepared using the method described in Example 403H starting with the compound described in Example 1166A and cyclohexanecarboxaldehyde. m/e (ESI) 613 (MH⁻)

Example 1170B

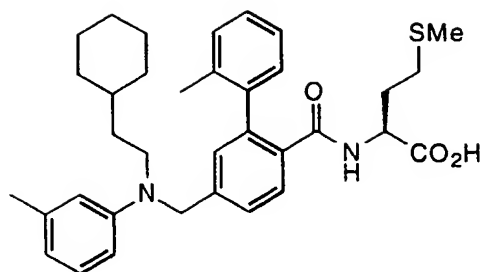
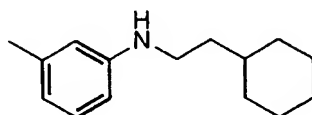
N-[4-N-(2-Butylphenyl)-N-(cyclohexylmethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

13510

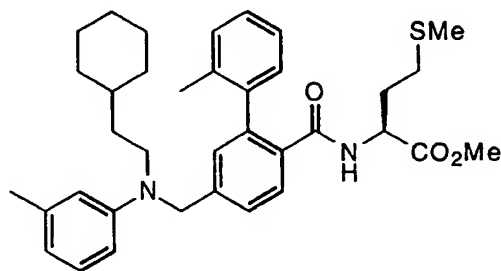
The desired compound was prepared according to the method of Example 403I starting with compound prepared in Example 1170A. ¹H (300MHz, DMSO, δ) 7.47 (1H, d, J=9Hz), 7.29 (1H, m), 7.25-6.95 (9H, m), 6.90 (1H, m), 3.97 (2H, s), 3.16 (1H, m), 2.70 (4H, m), 2.10-1.85 (7H, m), 1.70 (3H, m), 1.60-1.40 (6H, m), 1.40-1.15 (4H, m), 1.05 (3H, m), 0.79 (5H, t, J=8Hz). m/e (ESI) 599 (MH⁻) Anal.calc. for C₃₇H₄₇LiN₂O₃S·1.00 H₂O C 71.13, H 7.90, N 4.48 Found C 71.01, H 7.93, N 4.14

13515

13520

Example 1171Example 1171AN-(2-Cyclohexylethyl)-N-(3-methylphenyl)amine

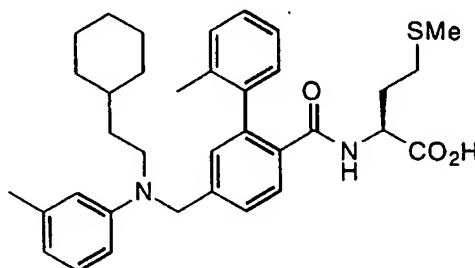
To a stirred solution at ambient temperature of cyclohexylacetic acid (500 mg, 3.52 mmol) and 3-methylaniline (0.45 mL, 4.22 mmol) in DMF (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (809 mg, 4.22 mmol). Reaction stirred overnight at ambient temperature. Reaction diluted with EtOAc and washed with water, 1.0M NaHCO₃ (2x), 1N H₃PO₄ (2x), and brine. Organic layer dried with Na₂SO₄, filtered, and concentrated in vacuo. To a solution at ambient temperature under N₂ of this residue in anhydrous THF (3 mL) was added a 1.0M lithium aluminum hydride solution (7.00 mL, 7 mmol) in THF. Reaction refluxed overnight. Reaction cooled to 0°C and quenched with successive addition of water (0.27 mL), 15% aqueous NaOH (0.27 mL), and water (0.80 mL). Mixture stirred 30 minutes at ambient temperature, and solids filtered off through celite and washed with EtOAc. Filtrate dried with Na₂SO₄, filtered, and concentrated in vacuo to produce a colorless oil. m/e (DCI/NH₃) 218 (MH⁺)

Example 1171B

13540

N-[4-N-(2-Cyclohexylethyl)-N-(3-methylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired ester was prepared using the method described in Example 403H starting
13545 with the compounds described in Example 403G and Example 1171A. m/e (ESI) 585 (MH⁺)

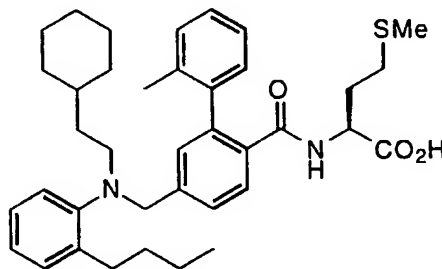


Example 1171C

N-[4-N-(2-Cyclohexylethyl)-N-(3-methylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

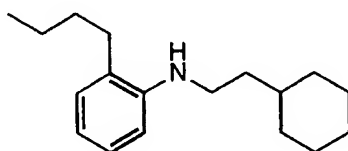
13550

The desired compound was prepared according to the method of Example 403I starting with compound prepared in Example 1171B. ¹H (300MHz, CDCl₃, δ) 7.92 (1H, t, J=9Hz), 7.40-7.00 (8H, m), 6.47 (2H, m), 5.86 (1H, d, J=8Hz), 4.51 (4H, m), 3.39 (2H, m), 2.25 (3H, s), 2.15-1.80 (8H, m), 1.70 (5H, m), 1.50 (3H, m), 1.40-1.05 (4H, m), 0.96 (2H, m). m/e (ESI) 571 (MH⁺) Anal.calc. for C₃₅H₄₄N₂O₃S·1.00 H₂O C 71.15, H 7.85, N 4.74 Found C 70.91, H 7.89, N 4.46
13555



13560

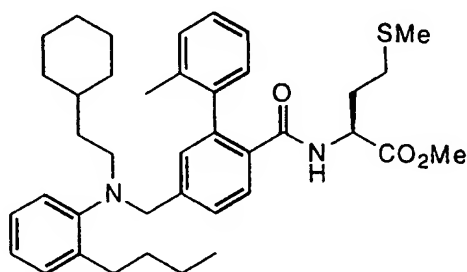
Example 1172



Example 1172A

N-(2-Butylphenyl)-N-(2-cyclohexylethyl)amine

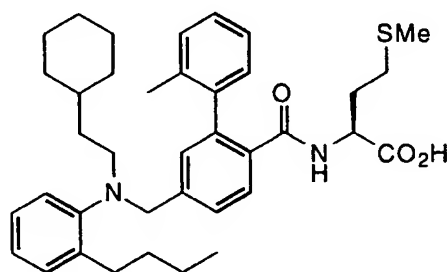
13565 The desired amine was prepared using the method described in Example 1171A starting with cyclohexylacetic acid and 2-butylaniline. m/e (DCI/NH₃) 260 (MH⁺)



Example 1172B

13570 N-[4-N-(2-Butylphenyl)-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired ester was prepared using the method described in Example 403H starting with the compounds described in Example 403G and Example 1172A. m/e (ESI) 627 (MH⁻)



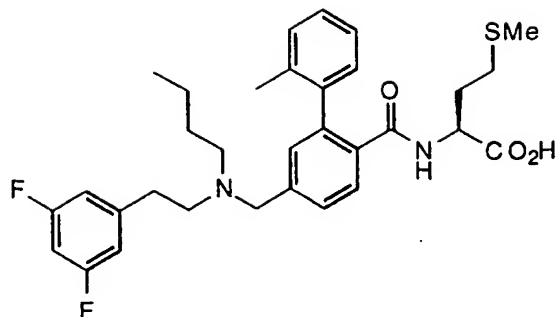
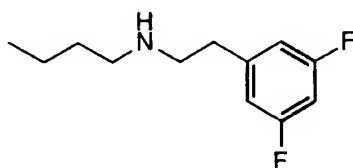
13575

Example 1172C

N-[4-N-(2-Butylphenyl)-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

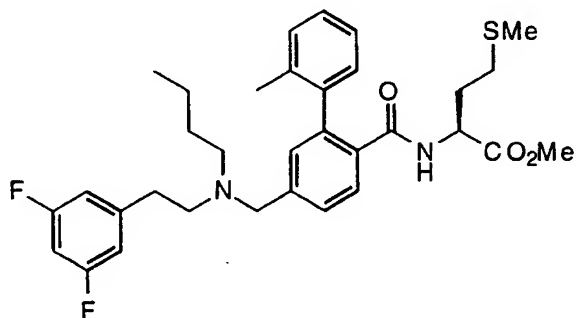
13580 The desired compound was prepared according to the method of Example 403I starting with compound prepared in Example 1172B. ¹H (300MHz, CDCl₃, δ) 7.94 (1H, t, J=9Hz), 7.41 (1H, bd, J=8HZ), 7.40-7.00 (9H, m), 5.85 (1H, dd, J=8&2Hz), 4.55 (1H, m), 4.07 (2H, s), 2.91 (2H, m), 2.68 (2H, m), 2.20-1.80 (9H, m), 1.70-1.40 (8H, m), 1.40-1.00 (8H, m), 0.86 (3H, t, J=8Hz), 0.79 (2H, m). m/e (ESI) 613 (MH⁻) Anal.calc. for C₃₈H₅₀N₂O₃S·0.25 H₂O C 73.69, H 8.22, N 4.52 Found C 73.74, H 8.17, N 4.30

13585

Example 1173Example 1173A

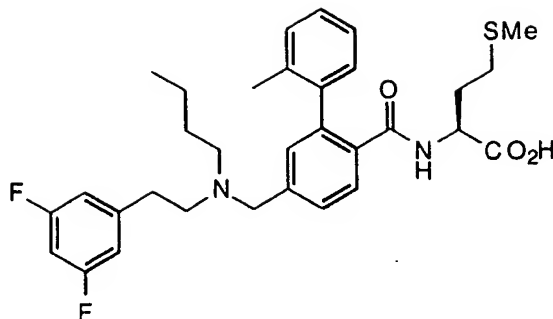
N-(2-Butylphenyl)-N-(2-(3,5-difluorophenylethyl)amine

The desired amine was prepared using the method described in Example 1171A starting with 3,5-difluorophenylacetic acid and butylamine. m/e (DCI/NH₃) 214 (MH⁺)

Example 1173B

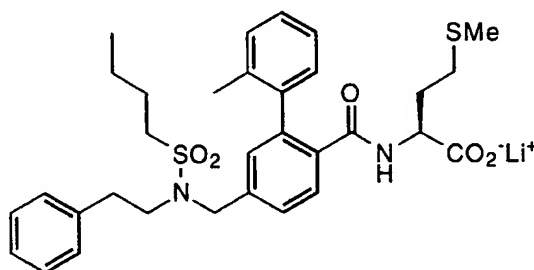
N-[4-N-Butyl-N-(2-(3,5-difluorophenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired ester was prepared using the method described in Example 403H starting with the compounds described in Example 403G and Example 1173A. m/e (ESI) 581 (MH⁺)

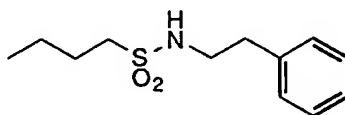
Example 1173C

13605 N-[4-N-Butyl-N-(2-(3,5-difluorophenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I starting with compound prepared in Example 1173B. ^1H (300MHz, CDCl_3 , δ) 7.80 (1H, d, $J=9\text{Hz}$), 7.54 (1H, m), 7.40-7.00 (5H, m), 6.80-6.60 (3H, m), 6.17 (1H, m), 4.43 (1H, m), 4.00 (2H, m), 2.98 (4H, m), 2.81 (2H, m), 2.20-1.80 (9H, m), 2.60 (3H, m), 1.30 (2H, m), 0.92 (3H, t, $J=8\text{Hz}$). m/e (ESI) 567 (MH^+) Anal. calc. for $\text{C}_{32}\text{H}_{38}\text{F}_2\text{N}_2\text{O}_3\text{S}^-$ 0.50 H_2O C 66.53, H 6.80, N 4.85 Found C 66.67, H 6.67, N 4.69



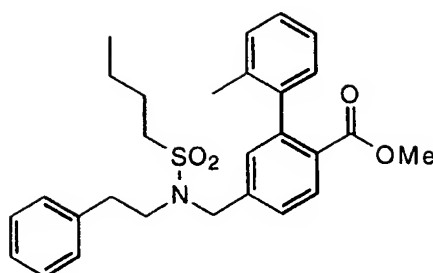
13615

Example 1174Example 1174A

13620 N-(Butanesulfonyl)-N-(2-phenylethyl)amine

To a stirred solution at ambient temperature of phenethylamine (200 mg, 1.65 mmol) in CH_2Cl_2 (2 mL) was added triethylamine (0.35 mL, 2.48 mmol) and butanesulfonyl chloride (0.24 mL, 1.82 mmol). After 4 hours of stirring at ambient temperature, the reaction was diluted with EtOAc and washed with water, 1.0M NaHCO_3 , and brine.

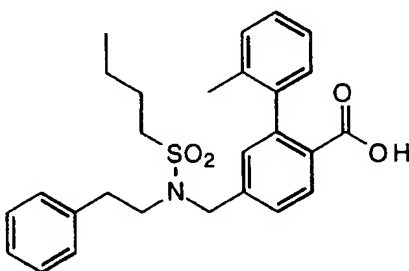
13625 Organic layer dried with Na_2SO_4 , filtered, and concentrated in vacuo.

Example 1174B4-(N-Butanesulfonyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester

13630

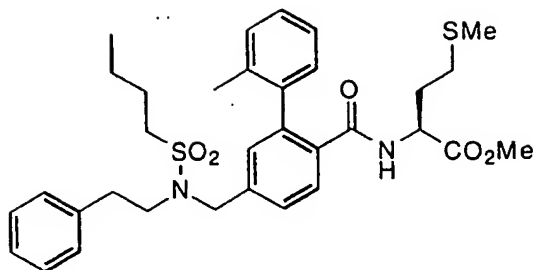
To a stirred mixture in anhydrous DMF (1 mL) at room temperature under N₂ of 60% sodium hydride suspension in mineral oil (30 mg, 0.752) was added N-(butanesulfonyl)-N-(2-phenylethyl)amine (181 mg, 0.752 mmol), prepared as in Example 1174A. Reaction stirred 20 minutes, and then, a solution of 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester (200 mg, 0.627 mmol), prepared as in Example 1178A-D, in anhydrous DMF (5 mL) was added. Reaction stirred overnight at room temperature. Reaction quenched with 1N H₃PO₄ and diluted with EtOAc. Organic layer separated, washed with brine, dried with Na₂SO₄, filtered, and concentrated in vacuo. Residue purified by flash chromatography on silica gel (15% EtOAc/Hexanes) to afford the desired product as a pale yellow oil (293 mg, 98%). m/e (ESI) 480 (MH⁺)

13640

Example 1174C4-(N-Butanesulfonyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoic acid

13645

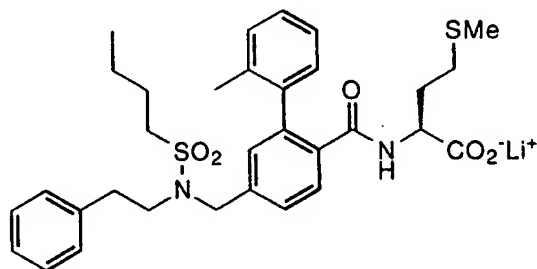
The desired acid was prepared using the method described in Example 403E starting with the product from Example 1174B.

Example 1174D

13650

N-[4-N-Butanesulfonyl-N-(2-phenylethyl)aminomethyl]-2-(2-methylphenyl)benzoylmethionine methyl ester

The desired compound was prepared using the method described in Example 403F starting with the product from Example 1174C. m/e (ESI) 480 (MH⁺)

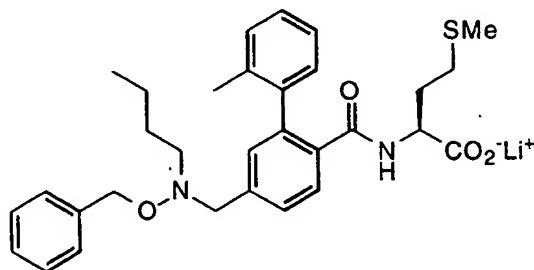


13655

Example 1174EN-[4-N-Butanesulfonyl-N-(2-phenylethyl)aminomethyl]-2-(2-methylphenyl)benzoylmethionine lithium salt

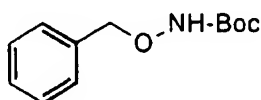
The desired compound was prepared according to the method of Example 403I starting with compound prepared in Example 1174D. ¹H (300MHz, DMSO-d₆, δ) 7.62 (1H, d, J=7Hz), 7.52 (1H, dd, J=7&2Hz), 7.20-7.10 (10H, m), 7.14 (1H, bd, J=7Hz), 4.65 (2H, bs), 3.76 (1H, m), 3.00 (2H, m), 2.78 (2H, m), 2.25-2.00 (5H, m), 1.99 (3H, s), 1.90-1.70 (4H, m), 1.62 (2H, m), 1.37 (2H, m), 0.92 (3H, t, J=8Hz). m/e (ESI) 595 (MH⁺) Anal.calc. for C₃₂H₃₉LiN₂O₅S₂·0.50 H₂O C 62.83, H 6.59, N 4.38 Found C

13665 62.59, H 6.59, N 4.44



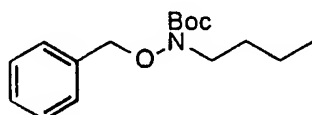
Example 1175

13670 *N*-[4-*N*--Benzyloxy-*N*-butylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

Example 1175A

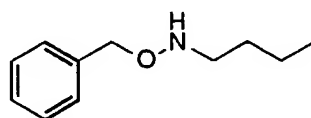
13675 *N*--t-Butoxycarbonyl-*O*-benzylhydroxylamine

To a stirred solution at 0°C of *O*-benzylhydroxylamine hydrochloride in THF was added diisopropylethylamine (2.5 equiv.) and di-*t*-butyldicarbonate (1.2 equiv.). Reaction stirred one hour at 0°C and overnight at ambient temperature. Reaction concentrated *in vacuo*. Residue taken up in EtOAc and washed with water, 1.0M NaHCO₃, 1N H₃PO₄, and brine. Organic layer dried with Na₂SO₄, filtered, and evaporated.

Example 1175B

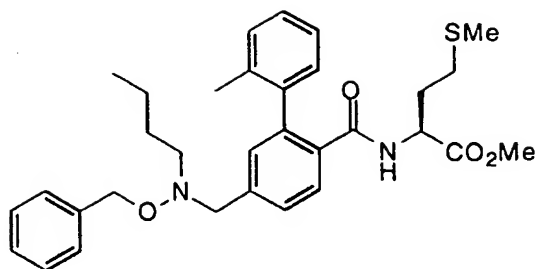
N--t-Butoxycarbonyl-*N*-butyl-*O*-benzylhydroxylamine

13685 To a stirred solution at 0°C of *N*--t-Butoxycarbonyl-*O*-benzylhydroxylamine, prepared as in Example 1175A, in anhydrous THF was added portionwise a 60% dispersion of sodium hydride (1.2 equiv.) in mineral oil. Mixture stirred 30 minutes at 0°C, and then, 1-iodobutane (1.2 equiv.) was added dropwise. Reaction stirred one hour at 0°C, and then, overnight at room temperature. Reaction concentrated *in vacuo*. Residue taken up in EtOAc and washed with water, 1.0M NaHCO₃, 1N H₃PO₄, and brine. Organic layer dried with Na₂SO₄, filtered, and evaporated.

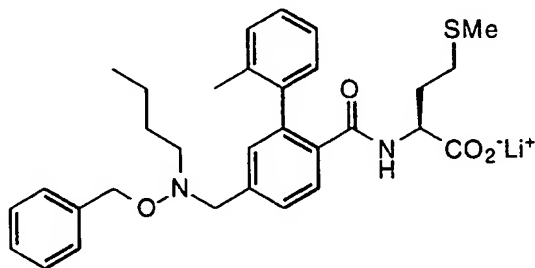
Example 1175C

13695 *N*-Butyl-*O*-benzylhydroxylamine hydrochloride salt

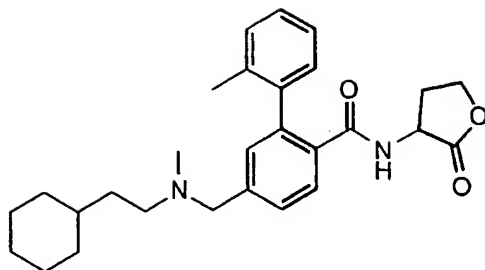
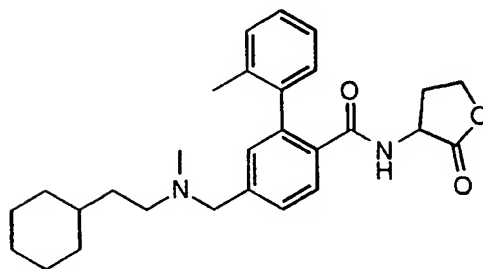
The desired compound was prepared using the method described in Example 403D starting with the compound prepared in Example 1175B.

Example 1175D*N*-[4-*N*--Benzyloxy-*N*-butylaminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired ester was prepared using the method described in Example 403H starting with the compound prepared in Example 1175C and *N*-[4-Formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, prepared as in Example 403G. *m/e* (ESI) 547 (MH⁻)

Example 1175E*N*-[4-*N*--Benzyloxy-*N*-butylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

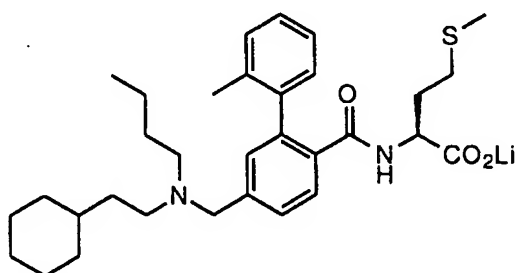
The desired compound was prepared according to the method of Example 403I starting with the compound in Example 1175D. ¹H (300MHz, DMSO-d₆, δ) 7.52 (1H, d, J=9Hz), 7.40 (1H, dd, J=7&2Hz), 7.30-7.10 (10H, m), 6.96 (1H, bd, J=7Hz), 4.46 (2H, bs), 3.87 (2H, bs), 3.71 (1H, m), 2.68 (2H, t, J=8Hz), 2.25-1.95 (5H, m), 1.93 (3H, s), 1.90-1.60 (2H, m), 1.50 (2H, m), 1.30 (2H, m), 0.83 (3H, t, J=8Hz). *m/e* (ESI) 533 (MH⁻) Anal.calc. for C₃₁H₃₇LiN₂O₄S·0.75 H₂O C 67.19, H 7.00, N 5.05 Found C 67.19, H 6.91, N 4.96

Example 1177Example 1177

N-[4-N-(2-Cyclohexylethyl)-N-methylaminomethyl]-2-(2-methylphenyl)benzoyl-3-aminotetrahydrofuran-2-one

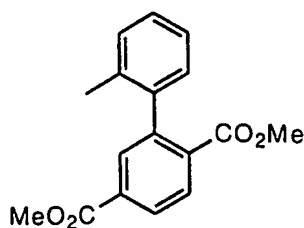
The desired compound was prepared using the method of Example 403F starting with 4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid, prepared as in Example 608C, and α -amino- γ -butyrolactone hydrobromide.

^1H (300MHz, CDCl_3 , δ) (rotamer) 7.91 (1H, t, $J=9\text{Hz}$), 7.41 (1H, bd, $J=8\text{Hz}$), 7.35-7.20 (4H, m), 7.19 (1H, d, $J=2\text{Hz}$), 5.72 (1H, m), 4.49 (1H, m), 4.33 (1H, bt, $J=8\text{Hz}$), 4.17 (1H, m), 3.53 (2H, s), 2.62 (1H, m), 2.39 (2H, t, $J=8\text{Hz}$), 2.20 (3H, s), 2.15 (2.07) (3H, s), 1.80-1.50 (7H, m), 1.38 (2H, m), 1.30-1.10 (3H, m), 0.89 (2H, m). m/e (ESI) 447 (MH^+) Anal.calc. for $\text{C}_{28}\text{H}_{36}\text{N}_2\text{O}_3 \cdot 1.00 \text{ H}_2\text{O}$ C 72.07, H 8.21, N 6.00 Found C 72.12, H 8.03, N 5.76

Example 1178

N-[4-(*N*-(2-cyclohexylethyl)-*N*-butylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,

Lithium Salt



13745

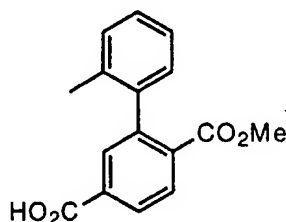
Example 1178A

Dimethyl-(2-methylphenyl)terephthalate

A mixture of dimethyliodoterephthalate (278 g, 0.87 mol), 2-methylphenylboronic acid (141 g, 1.04 mol) palladium (II) acetate (1.95 g, 0.0087 mol) and triphenylphosphine (9.1 g, 0.035 mol) in 2.2 L of toluene and 2.2 L of 2M sodium carbonate was degassed with nitrogen and heated to 80°C for 1.5 hours and cooled to ambient temperature. The layers were separated and the organic layer filtered through a plug of silica gel (600g) prewetted with methyl t-butylether (MTBE, 1.2 L). The frit was washed with 5 L of MTBE. The mixture was then concentrated to provide 237 g (96%) of the title compound. ¹H NMR (CDCl₃) δ 8.09, dd, 1H; 8.02, d, 1H; 7.95, d, 1H; 7.20 - 7.34, m, 3H; 7.10, bd, 1H; 3.96, s, 3H; 3.64, s, 3H; 2.08, s, 3H. MS (DCI/NH₃) 302 (M + NH₄)⁺.

13750

13755



Example 1178B

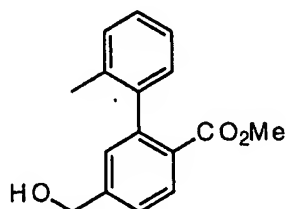
2-(2-methylphenyl)-4-carboxybenzoic acid, methyl ester

13760

13765

A solution of example 1178A (194 g, 0.68 mol) in 2:1 THF/methanol (~0.3M) was cooled to 0°C and lithium hydroxide (0.38 L of a 2.2 M aqueous solution, 0.82 mol) was added such that the reaction temperature remained below 10°C. The cooling bath was removed and the mixture allowed to warm to 11°C overnight and then warmed to ~ 20°C over 4 hours. The mixture was concentrated to a volume of ~ 1.2 L and then diluted to 5.6 L with water. The mixture was extracted with hexanes and the aqueous layer filtered through celite (~200 g) and the celite pad washed with water. The mixture was diluted with ethyl acetate (6 L) and the pH of the aqueous phase adjusted to 5.5 by the addition of 3M aqueous HCl (~ 250 mL). The organic phase was removed and concentrated to provide 171 g (93%) of the

13770 title compound. The material was ~ 87% pure. An analytical sample was obtained by recrystallization from aqueous ethanol. ^1H NMR (CDCl_3) δ 8.14, dd, 1H; 8.03, d, 1H; 8.01, d, 1H; 7.28 - 7.42, m, 3H; 7.09, bd, 1H; 3.64, s, 3H; 2.08, s, 3H. MS (DCI/NH_3): 271 (MH^+); 288 ($\text{M} + \text{NH}_4^+$).



13775

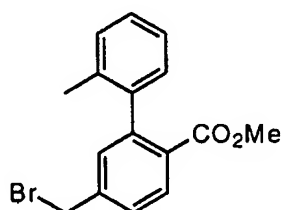
Example 1178C

4-hydroxymethyl-2-(2-methylphenyl)benzoic, methyl ester

13780 A solution of example 1178B (4.67g, 17.3 mmol) in 35 mL of THF was cooled in an ice bath and treated with borane (0.88M in THF, 39 mL, 34.6 mmol) such that the internal temperature remained below 10°C. The cooling bath was removed and the solution stirred for 3 hours and then cooled in an ice bath. The reaction was quenched by the careful addition of 8 mL of water (vigorous evolution of hydrogen gas) keeping the temperature below 10°C. An additional 8 mL of water was added and the mixture partitioned between

13785 ethyl acetate and 2N sodium hydroxide. The layers were separated and the organic layer was extracted with water, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel to provide 3.90 g (88%) of the title compound. ^1H NMR (CDCl_3) δ 7.98, d, 1H; 7.43, dd, 1H; 7.16 - 7.28, m, 4H; 7.07, bd, 1H; 4.77, s, 2H; 3.62, s, 3H; 2.05, s, 3H; 1.78, bs, 1H. MS (DCI/NH_3): 257 (MH^+); 274 ($\text{M} + \text{NH}_4^+$).

13790

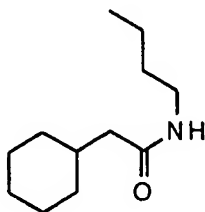


Example 1178D

4-bromomethyl-2-(2-methylphenyl)benzoic, methyl ester

13795 A solution of 36 g (140 mmol) of example 1178C and 13.4 g (154 mmol) lithium bromide in DMF (150 mL) was chilled in an ice-water bath, then 40.3 g (14.0 mL, 149 mmol) phosphorous tribromide was added, followed by more DMF (50 mL). After 15 minutes the reaction was partitioned between water (1200 mL) and Et_2O (600 mL). The aqueous layer was extracted with Et_2O (2 x 150 mL), then the combined Et_2O layers were

13800 washed with brine, and dried over Na₂SO₄. After filtration and concentration, recovered 44.5 g (97.5%) slightly cloudy, almost colorless oil that was 2% DMF by weight (determined by NMR). ¹H NMR (CDCl₃) δ 7.84 (d, 1H), 7.44 (dd, 1H), 7.24 (m, 4H), 7.07 (br d, 1H), 4.50 (s, 2H), 3.62 (s, 3H), 2.07 (s, 3H). MS (DCI/NH₃) 336/338 (M+H+NH₃)⁺.



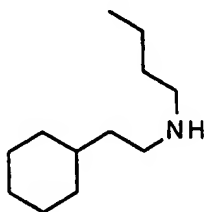
13805

Example 1178E

N-butyl-N-2-cyclohexylacetamide

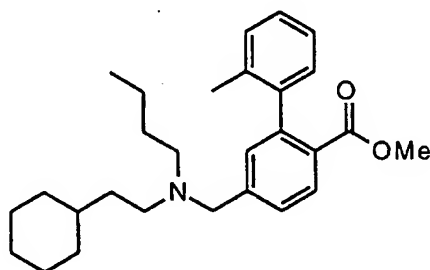
2-Cyclohexylacetic acid (42.66 g, 0.30 mol) was dissolved in 85 mL of thionyl chloride and the mixture heated to reflux for 2 hours. After cooling to room temperature, the yellow solution was concentrated. Toluene was added and the solution was concentrated again and the acid chloride used directly. The acid chloride was diluted with 100 mL of methylene chloride and this solution added to a biphasic mixture of butylamine (60 mL, 0.60 mol) in 100 mL of methylene chloride and 2M aqueous potassium carbonate (150 mL) and the mixture was stirred overnight at ambient temperature. An additional 30 mL of butylamine was added and stirring continued for 2 hours and then the mixture was poured into a separatory funnel. The layers were separated and the aqueous phase was extracted with 1 portion of methylene chloride and the combined organic extracts were dried, filtered and concentrated to an off white solid. This material was suspended in 400 mL of 1:1 ether/hexanes and filtered. The solid was washed with 2 additional portions of 1:1 ether/hexanes. The filtrates were extracted with 3 portions of aqueous HCl, dried, filtered and concentrated to a volume of ~ 200 mL. The solid that formed was collected by filtration and combined with the previous solid material and dried under vacuum to give the title compound (49.50 g, 88%). ¹H nmr (300 MHz., CDCl₃): δ 5.35, bs, 1H; 3.24, q, 2H; 2.02, d, 2H; 1.70, bm, 6H; 1.47, m, 2H; envelope 1.06 - 1.42, 5H; 0.91, m, 5H. MS (DCI-NH₃): 198 (MH⁺); 215 (M+NH₄⁺).

13825



Example 1178FN-butyl-N-2-cyclohexylethylamine

13830 A stirred suspension of lithium aluminum hydride (23.74 g, 0.63 mol) in THF (400 mL) was cooled in an ice bath and treated with a solution of example 1178E (49.50 g, 0.26 mol) in THF (300 mL). The ice bath was removed and the mixture heated to gentle reflux for 20 hours. The solution was cooled in an ice bath and quenched by the careful addition of 24 mL of water in 100 mL of THF, followed by 24 mL of 15% aqueous sodium hydroxide, 13835 followed by an additional 72 mL of water. The thick slurry was vigorously stirred for 15 minutes at which time 600 mL of methylene chloride and excess sodium sulfate were sequentially added. The mixture was stirred for 1 hour and then filtered through celite. The celite pad was washed well with methylene chloride and the filtrate concentrated to give the title compound (47.80 g, 100%) which was sufficiently pure for the next step. ¹H nmr (300 13840 MHz., CDCl₃): δ 2.61, m, 4H; 1.69, m, 5H; envelope 1.05 - 1.53, 11H; 0.91, m, 5H. MS (DCI-NH₃): 184 (MH⁺).

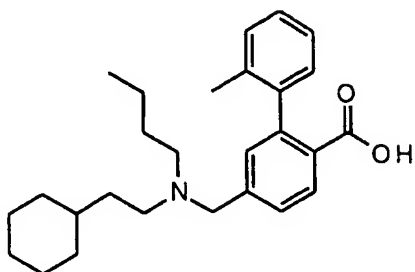
Example 1178G

13845 4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoic acid, methyl ester

A solution of example 1178D (22.2 g, 0.070 mol) and diisopropylethylamine (15.7 mL, 0.090 mol) in 100 mL of acetonitrile was treated with N-butyl-N-2-cyclohexylethylamine (15.3 g, 0.084 mol). The cloudy mixture was stirred for two hours 13850 and then briefly warmed to ~45°C. After cooling to ambient temperature, the mixture was concentrated to remove the acetonitrile and then diluted with 400 mL of water. The pH of the mixture was brought to >10 with solid potassium phosphate and extracted with 3 portions of ethyl ether. The combined ether extracts were extracted with 1 portion of water and two 13855 portions of brine, dried, filtered and concentrated. The residue obtained (34.4 g, 117%) was used directly. An analytical sample was obtained by column chromatography on silica gel (3% ethyl acetate/hexanes) to provide pure material. ¹H nmr (300 MHz., CDCl₃): δ 7.92, d, 1H; 7.48, dd, 1H; 7.16 - 7.28, m, 4H; 7.07, bd, 1H; 3.62, s, 3H; 3.57, s, 2H; 2.41,

quartet, 4H; 2.06, s, 3H; 1.62, bm, 5H; envelope 1.05 - 1.48, 10H; 0.85, bm, 5H. MS (ESI+): 422 (MH⁺); (ESI-): 420 (M-H).

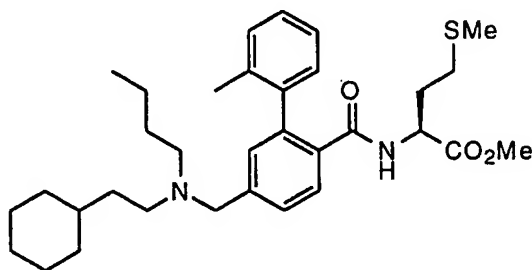
13860



Example 1178H

N-[4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)]benzoic acid

13865 A solution of 1178G (34.35 g, 0.081 mol) in 210 mL of ethanol was treated with aqueous sodium hydroxide (4N, 70 mL, 0.28 mol) and the mixture heated to reflux until judged complete by tlc analysis. After cooling to room temperature, the mixture was concentrated to remove the ethanol. The resulting solid was partially dissolved by adding water and the mixture extracted with ethyl ether. The ether layer was then washed with water and then with 1M aqueous phosphoric acid which resulted in an oily precipitate. The
13870 precipitate was dissolved by extracting with 3 portions of ethyl acetate and the combined ethyl acetate layer were washed with water, 0.5M aqueous phosphoric acid, brine and then dried, filtered and concentrated to give 24.5 g, (86% yield for the two steps) as a cream colored solid. ¹H nmr (300 MHz., CD₃OD): δ 7.96, d, 1H; 7.64, dd, 1H; 7.37, d, 1H; 7.22, m, 2H; 7.18, m, 1H; 7.07, d, 1H; 4.41, bs, 2H; 3.12, m, 4H; 2.10, s, 3H; 1.18, bm,
13875 9H; 1.37, sextet, 2H; 1.23, m, 3H; 0.96, t, 3H; 0.94, m, 2H. MS (ESI+): 408 (MH⁺); (ESI-): 406 (M-H).

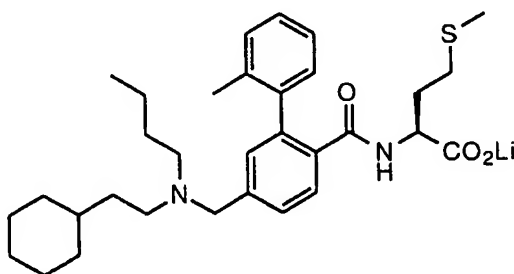


Example 1178I

N-[4-(N-Butyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

Partitioned 13.2 g (66.1 mmol) L-methionine methyl ester, hydrochloride salt between saturated aqueous NaHCO₃ (80 mL) and CH₂Cl₂ (75 mL). Added the organic

layer to the following solution: 24.5 g (60.2 mmol) acid from Example 1178H, 10.0 g (65.3 mmol) HOBT•H₂O, and 12.6 g (65.7 mmol) EDCI•HCl in DMF (150 mL). After stirring at RT overnight partitioned the reaction between saturated aqueous NaHCO₃ (500 mL) and EtOAc (1200 mL). The organic layer was washed with water and brine, then dried over Na₂SO₄. After filtration and concentration, recovered 30 g orange oil that was purified by chromatography using hex/EtOAc 3/1. Recovered 22.9 g (69%) of the title compound. ¹H NMR (CDCl₃) δ 7.90 (m, 1H), 7.40 (d, 1H), 7.30, 7.20, 7.16 (all m, total 5H), 5.88 (br d, 1H), 4.62 (m, 1H), 3.66 (s, 3H), 3.57 (s, 2H), 2.41 (m, 4H), 2.18, 2.13, 2.04 (s, m, m, total 9H), 1.85 (m, 1H), 1.62 (m, 5H), 1.50-1.10 (envelope, 10H), 0.87 (m, 5H). MS (APCI) 553 (M+H)⁺.

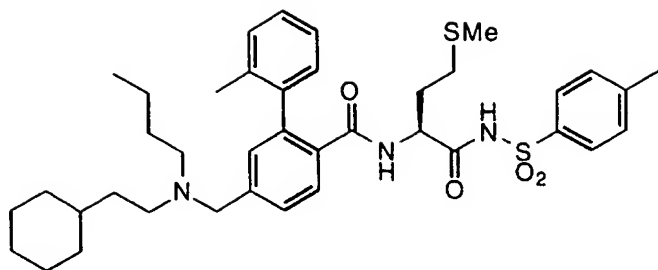
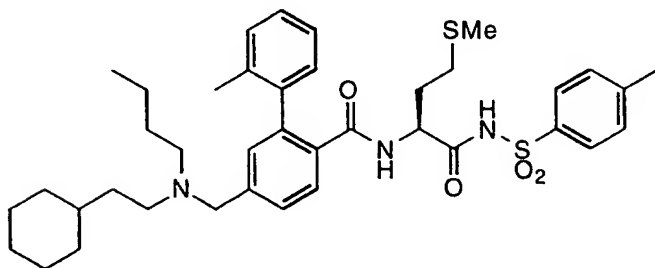


Example 1178J

N-[4-(*N*-(2-cyclohexylethyl)-*N*-butylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine.
Lithium Salt

A solution of example 1178I (22.9 g, 0.041 mol), in 200 mL of 3:1 THF methanol was cooled in an ice bath and then treated with aqueous lithium hydroxide (1M, 83 mL, 0.083 mol) dropwise. The ice bath was removed and the mixture was stirred for 20 hours. The solution was concentrated to remove the organics and the resulting thick slurry diluted with water until a clear solution resulted (~1.2 L). The pH of the solution was carefully adjusted to pH~5 with 1M aqueous phosphoric acid and stirred for 1 hour. The solid was collected by filtration and dried under vacuum over phosphorous pentoxide to provide 19.93 g of a cream colored solid. This material was dissolved in 200 mL of THF and treated with a solution of 1.55 g (0.037 mol) of lithium hydroxide in 75 mL of water. The mixture was stirred for 15 minutes and the THF removed under vacuum on a rotary evaporator. The mixture was diluted with 500 mL of water and lyophilized to give 20.10 g (89% overall) of the title compound. ¹H nmr (300 MHz., CD₃OD): δ 7.64, m, 1H; 7.41, d, 1H; 7.05 - 7.32, m, 5H; 4.25, m, 1H; 3.69, s, 2H; 2.52, m, 4H; 2.51, s, 1.5H (1/2 o-tolyl); 2.06, s, 1.5 H (1/2 o-tolyl); 1.98, s, 3H; 1.97, m, 1H; 1.73, m, 2H; 1.64, bm, 6H; envelope 1.04 - 1.56, 10H; 0.90, m, 5H. MS (ESI⁺): 539 (MH⁺); (ESI⁻): 537 (M-H). Calc'd for C₃₂H₄₅N₂O₃SLi•0.60 H₂O; C 69.19; H 8.38; N 5.04; Found: C 69.25; H 8.50; N 4.99.

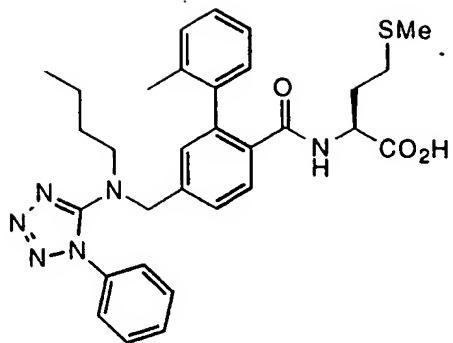
13915

Example 1179Example 1179

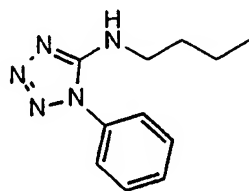
N-[4-N-Butyl-N-(2-cyclohexylethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine
4-methylphenylsulfonimide

N-[4-(N-Butyl-N-(2-Cyclohexylethyl)aminomethyl)-2-(2-

13925 methylphenyl)benzoyl]methionine (500 mg, 0.929 mmol), prepared as in Example 1178, p-toluenesulfonamide (429 mg, 2.51 mmol), 4-dimethylaminopyridine (57 mg, 0.465 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (214 mg, 1.12 mmol) were dissolved in CH₂Cl₂ (10 mL) at room temperature and stirred overnight. Reaction diluted with water and CHCl₃ and layers separated. Aqueous layer extracted with CHCl₃ (2x), and combined
 13930 extracts dried with Na₂SO₄, filtered, and concentrated in vacuo. Residue purified by flash chromatography on silica gel eluting with 300:1 EtOAc/25:1:1 EtOAc, H₂O, AcOH to afford the desired compound as a white solid (284 mg, 44%). ¹H (300MHz, MeOD, δ) (rotamer) 7.73 (2H, d, J=9Hz), 7.62 (1H, d, J=8Hz), 7.48 (1H, bd, J=8Hz), 7.30-7.00 (7H, m), 4.22 (1H, m), 4.02 (2H, bs), 2.81 (4H, m), 2.39 (3H, s), 2.21(2.03) (3H, bs),
 13935 1.90 (3H, s), 1.85-1.40 (13H, m), 1.40-1.10 (6H, m), 0.93 (5H, t, J=8Hz). m/e (ESI) 690 (MH⁺) Anal.calc. for C₃₉H₅₃N₃O₄S₂·1.25 H₂O C 65.56, H 7.83, N 5.88 Found C 65.41, H 7.52, N 5.61



13940

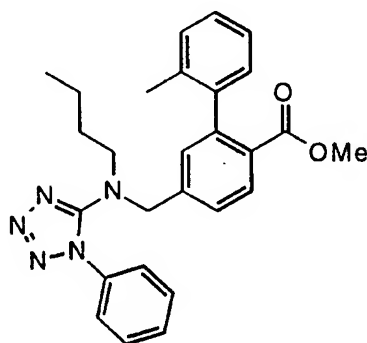
Example 1180Example 1180A

13945

N-Butyl-N-(1-phenyltetrazol-5-yl)amine

5-Chloro-1-phenyl-1H-tetrazole (1.00 g, 5.54 mmol), butylamine (0.547 mL, 5.54 mmol), and diisopropylethylamine (1.48 mL, 8.31 mmol) were dissolved in DMF (5 mL), and stirred overnight at room temperature. Reaction diluted with EtOAc and washed with water and brine. Organic layer dried with Na₂SO₄, filtered, and concentrated in vacuo. Residue purified by flash chromatography on silica gel eluting with 35% EtOAc/Hexanes to afford the desired product as a white solid (625 mg, 52%). m/e (DCI) 218 (MH⁺)

13950

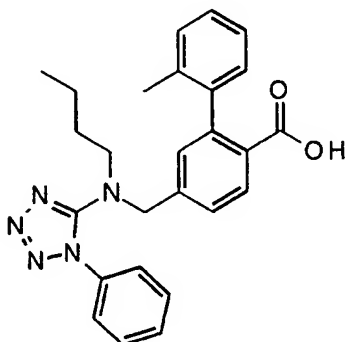
Example 1180B

13955

4-N-Butyl-N-(1-phenyltetrazol-5-yl)aminomethyl-2-(2-methylphenyl)benzoic acid methyl ester

The desired compound was prepared according to the method of Example 1174B starting with 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as in Example 1178A-D, and the compound from Example 1180A.

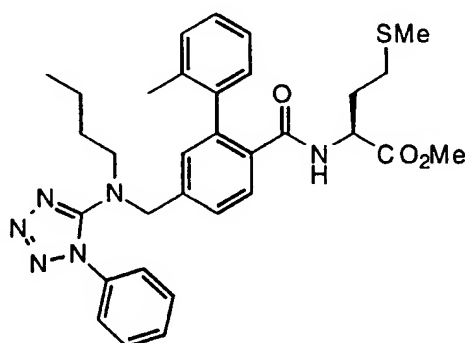
13960

Example 1180C

4-N-Butyl-N-(1-phenyltetrazol-5-yl)aminomethyl-2-(2-methylphenyl)benzoic acid

The desired acid was prepared using the method described in Example 403E starting with the product from Example 1180B. m/e (ESI) 440 (MH⁻)

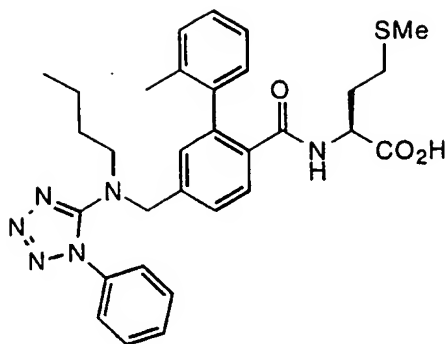
13965

Example 1180D

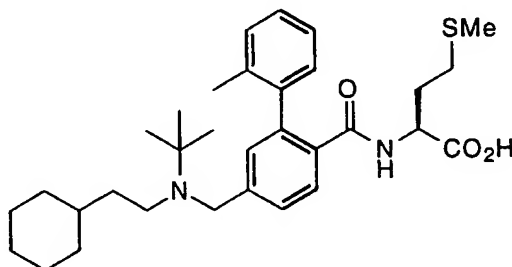
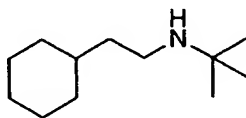
N-[4-N-Butyl-N-(1-phenyltetrazol-5-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

13970

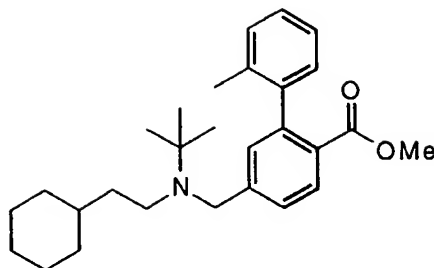
The desired compound was prepared using the method described in Example 403F starting with the product from Example 1180C. m/e (ESI) 587 (MH⁺)

Example 1180EN-[4-N-Butyl-N-(1-phenyltetrazol-5-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1180D. ^1H (300MHz, CDCl_3 , δ) 7.93 (1H, m), 7.60-7.40 (5H, m), 7.40-7.10 (5H, m), 7.03 (1H, d, $J=2\text{Hz}$), 5.89 (1H, m), 4.55 (1H, m), 4.52 (2H, s), 3.11 (2H, bt, $J=8\text{Hz}$), 2.20-2.00 (8H, m), 1.90 (1H, m), 1.56 (1H, m), 1.43 (2H, m), 1.06 (2H, m), 0.74 (3H, t, $J=8\text{Hz}$). m/e (ESI) 571 (MH^+) Anal.calc. for $\text{C}_{31}\text{H}_{36}\text{N}_6\text{O}_3\text{S}$ C 65.01, H 6.34, N 14.67 Found C 64.77, H 6.33, N 14.70

Example 1181Example 1181AN-t-Butyl-N-(2-cyclohexylethyl)amine

The desired amine was prepared using the method described in Example 1171A starting with cyclohexylacetic acid and t-butylamine. m/e (DCI/ NH_3) 184 (MH^+)



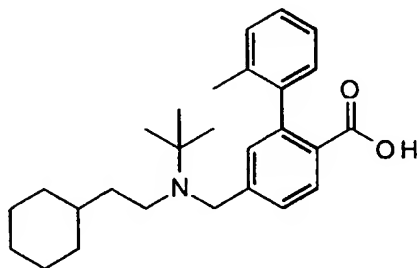
13995

Example 1181B

4-(N-t-Butyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester

14000

The desired compound was prepared using the method described in Example 1178G starting with N-t-butyl-N-(2-cyclohexylethyl)amine, prepared as in Example 1181A, and 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as in Example 1178A-D. m/e (ESI) 422 (MH⁺)

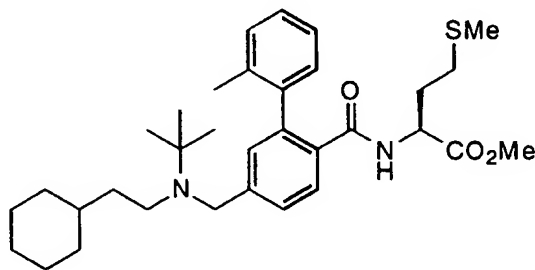


14005

Example 1181C

4-(N-t-Butyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoic acid

The desired acid was prepared using the method described in Example 403E starting with the compound prepared in Example 1181B.



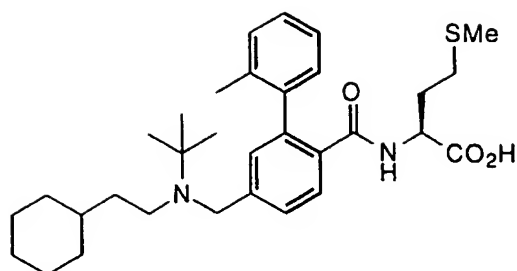
14010

Example 1181D

N-[4-(N-t-Butyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

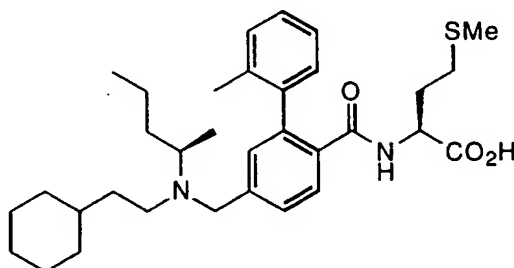
14015

The desired product was prepared using the method described in Example 403F starting with the compound prepared in Example 1181C. m/e (ESI) 553 (MH⁺)

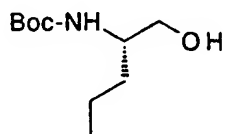
Example 1181E

N-[4-N-t-Butyl-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

14020 The desired compound was prepared according to the method of Example 403I
 starting with compound prepared in Example 1181D. ^1H (300MHz, CDCl_3 , δ) 7.78 (1H,
 m), 7.67 (1H, m), 7.40-7.00 (5H, m), 6.21 (1H, m), 4.38 (1H, m), 4.13 (2H, m), 2.93
 (2H, m), 2.20-2.00 (7H, m), 2.00 (3H, s), 1.60 (4H, m), 1.43 (12H, bs), 1.40-0.90 (4H,
 m), 0.75 (2H, m). m/e (ESI) 537 (MH^+) Anal. calc. for $\text{C}_{32}\text{H}_{46}\text{N}_2\text{O}_3\text{S} \cdot 0.75 \text{ H}_2\text{O}$ C
 14025 69.59, H 8.67, N 5.07 Found C 69.78, H 8.65, N 4.89

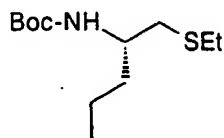
Example 1182

14030

Example 1182A

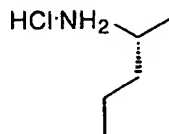
(2S)-t-Butoxycarbonylaminopentan-1-ol

14035 The desired product was prepared using the methods described in Example 1183A
 starting with L-norvaline.



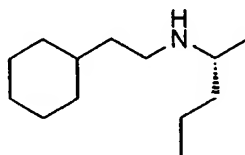
Example 1182B(2S)-t-Butoxycarbonylamino-1-ethylthiopentane

14040 The desired product was prepared using the methods described in Example 403B and 403C starting with the compound prepared in Example 1182A.

Example 1182C(2R)-Aminopentane hydrochloride salt

14045

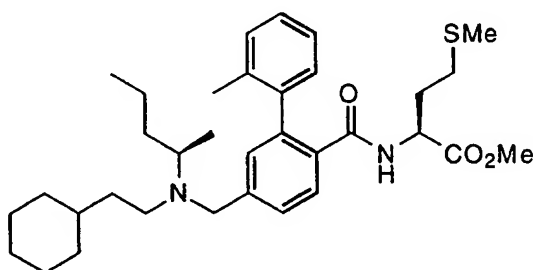
The desired product was prepared using the methods described in Example 1183C starting with the compound prepared in Example 1182B.

Example 1182DN-(2-Cyclohexylethyl)-N-(pent-2-yl)amine

14050

The desired amine was prepared using the method described in Example 1171A, except triethylamine was added, starting with cyclohexylacetic acid and the compound from Example 1182C. m/e (DCI) 198 (MH⁺)

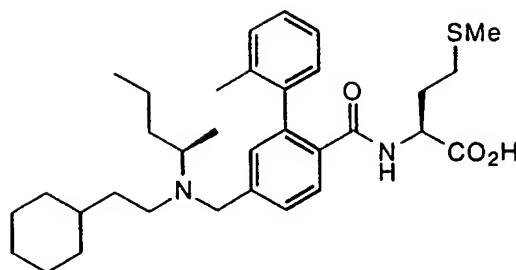
14055

Example 1182E

N-[4-N-(2-Cyclohexylethyl)-N-(pent-2-yl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

14060

The desired product was prepared using the method described in Example 403H starting with the compound prepared in Example 1182D and N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, prepared as in Example 403G. m/e (ESI) 567 (MH⁺)

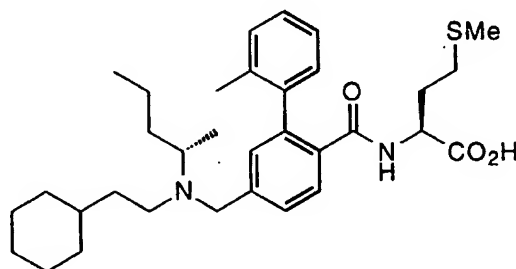
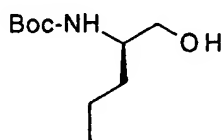


14065

Example 1182FN-[4-N-(2-Cyclohexylethyl)-N-(pent-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I starting with the compound prepared in Example 1182E. ^1H (300MHz, CDCl_3 , δ) 7.74 (1H, m), 7.62 (1H, m), 7.40-7.00 (5H, m), 6.46 (1H, m), 4.37 (1H, m), 3.94 (2H, m), 3.37 (1H, m), 2.90 (2H, m), 2.20-1.80 (8H, m), 1.80-1.60 (6H, m), 1.55-1.25 (6H, m), 1.25-1.00 (8H, m), 0.91 (3H, t, $J=8\text{Hz}$), 0.82 (2H, m). m/e (ESI) 551 (MH^+) Anal. calc. for $\text{C}_{33}\text{H}_{48}\text{N}_2\text{O}_3\text{S}\cdot 0.50\text{ H}_2\text{O}$ C 70.55, H 8.79, N 4.99 Found C 70.55, H 8.71, N 4.87

14075

Example 1183

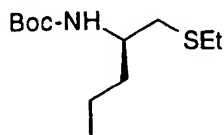
14080

Example 1183A(2R)-t-Butoxycarbonylaminopentan-1-ol

To a stirred solution at ambient temperature of D-norvaline (5.00 g, 42.7 mmol) in THF (100 mL) was added an aqueous 4N NaOH solution (21 mL, 84 mmol), di-t-butyl dicarbonate (11.2 g, 51.2 mmol), and tetrabutylammonium bromide (1.0 g). Two-phase solution stirred overnight at ambient temperature. Reaction neutralized with aqueous 3N HCl to pH 6 and extracted with CHCl_3 (3x). Extracts dried with Na_2SO_4 , filtered, and concentrated in vacuo to produce a colorless oil. To a stirred solution at 0°C under N_2 of the

14085

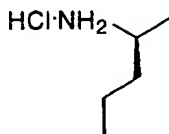
14090 crude residue in anhydrous THF (80 mL) was added dropwise via addition funnel a 1.0M
 borane-THF complex (100 mL, 100 mmol) in THF. After stirring overnight at ambient
 temperature, reaction cooled back to 0°C and quenched with an aqueous 4N NaOH solution
 (50 mL). Mixture stirred one hour at ambient temperature, and then, extracted with CH₂Cl₂
 (3x). Extracts dried with Na₂SO₄, filtered, and concentrated in vacuo. Residue purified by
 14095 flash chromatography on silica gel eluting with 30% EtOAc/Hexanes to afford the alcohol as
 a pale yellow oil (3.87 g, 45%). m/e (DCI) 204 (MH⁺)



Example 1183B

(2R)-t-Butoxycarbonylamino-1-ethylthiopentane

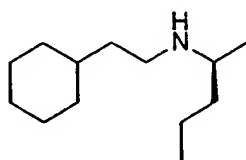
14100 The desired product was prepared using the methods described in Example 403B and
 403C starting with the compound prepared in Example 1183A. m/e (DCI) 248 (MH⁺)



Example 1183C

(2S)-Aminopentane hydrochloride salt

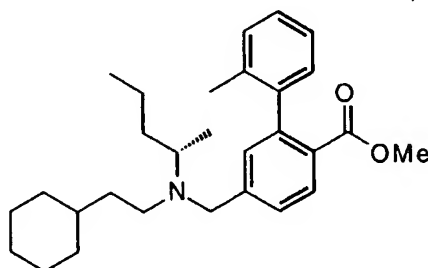
14105 To a stirred solution at ambient temperature of (2R)-t-butoxycarbonylamino-1-
 ethylthiopentane (655 mg, 2.65 mmol), prepared as in Example 1183B, in EtOH (5 mL)
 was added a 50% slurry of Raney Nickel (2.65 g) in water. Mixture stirred vigorously at
 80°C for 2 days. Reaction filtered through celite, and celite and catalyst washed with EtOAc.
 14110 Filtrate concentrated in vacuo to produce a colorless liquid. Residue taken up in a solution of
 4N HCl in dioxane (5 mL), and reaction stirred overnight at ambient temperature. Ether
 added until a solid precipitated. Solid filtered off, washed with ether, and dried to produce
 the desired compound as a white solid (167 mg, 59%).



Example 1183D

N-(2-Cyclohexylethyl)-N-(pent-2-yl)amine

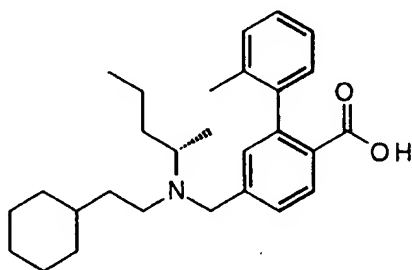
The desired amine was prepared using the method described in Example 1171A, except triethylamine was added, starting with cyclohexylacetic acid and the compound
 14120 from Example 1183C. ^1H NMR (CDCl_3 , 300 MHz) δ 2.70-2.50 (m, 4H), 1.80-1.60 (m, 6H), 1.50-1.00 (m, 8H), 1.04 (d, 3H, $J=8\text{Hz}$), 1.00-0.80 (m, 5H)



Example 1183E

14125 N-[4-N-(2-Cyclohexylethyl)-N-(pent-2-yl)aminomethyl]-2-(2-methylphenyl)benzoic acid methyl ester

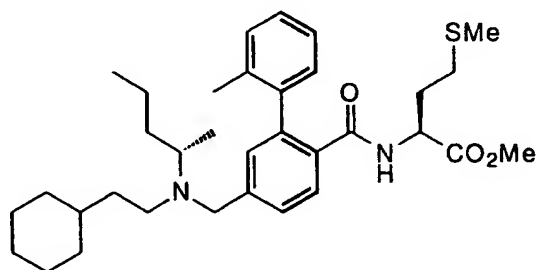
The desired compound was prepared using the method described in Example 1178G starting with N-(2-cyclohexylethyl)-N-(1-methylbutyl)amine, prepared as in Example 1183D, and 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as
 14130 in Example 1178A-D. m/e (ESI) 436 (MH^+)



Example 1183F

N-[4-N-(2-Cyclohexylethyl)-N-(pent-2-yl)aminomethyl]-2-(2-methylphenyl)benzoic acid

14135 The desired acid was prepared using the method described in Example 403E starting with the compound prepared in Example 1183E.

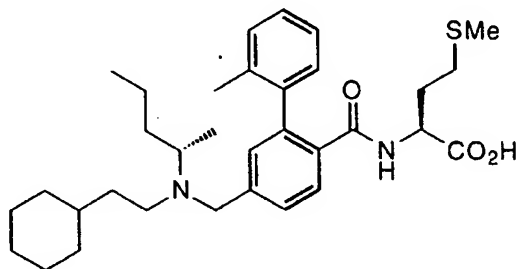


Example 1183G

14140

N-[4-N-(2-Cyclohexylethyl)-N-(pent-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired product was prepared using the method described in Example 403F starting with the compound prepared in Example 1183F. m/e (ESI) 567 (MH⁺)



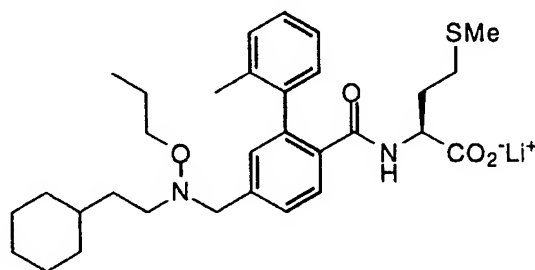
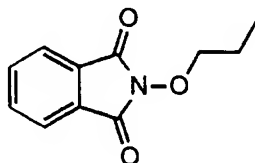
14145

Example 1183H

N-[4-N-(2-Cyclohexylethyl)-N-(pent-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1183G. ¹H (300MHz, CDCl₃, δ) 7.69 (2H, m), 7.40-7.00 (5H, m), 6.46 (1H, m), 4.38 (1H, m), 4.05 (2H, m), 3.41 (1H, m), 2.90 (2H, m), 2.20-1.75 (9H, m), 1.75-1.50 (7H, m), 1.50-1.00 (12H, m), 0.90 (5H, m). m/e (ESI) 551 (MH⁺) Anal. calc. for C₃₃H₄₈N₂O₃S·0.50 H₂O C 70.55, H 8.79, N 4.99 Found C 70.65, H 8.63, N 4.93

14155

Example 1184

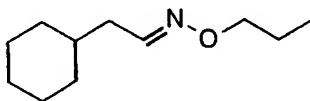
14160

Example 1184A

N-Propoxyphthalimide

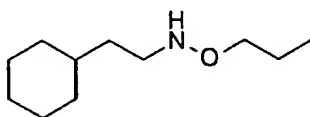
The desired product was prepared using the method described in Example 1176A starting with N-hydroxyphthalimide and 1-propanol. m/e (DCI) 223 (MH+NH₃⁺)

14165

Example 1184BO-Propyl-2-cyclohexylacetaldoxime

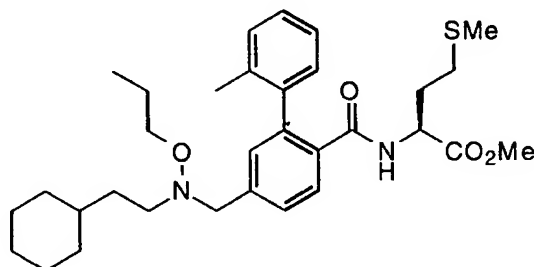
The desired product was prepared using the method described in Example 1176B starting with the compound from Example 1184 A and cyclohexylacetaldehyde.

14170

Example 1184CN--(2-Cyclohexylethyl)-N-propyloxyamine

The desired product was prepared using the method described in Example 1176C starting with the compound from Example 1184B. m/e (DCI) 186 (MH⁺)

14175

Example 1184D

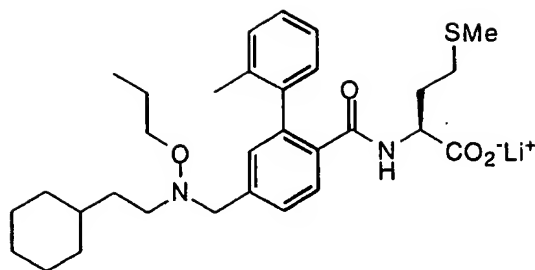
N-[4-N--(2-Cyclohexylethyl)-N-propyloxyaminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

14180

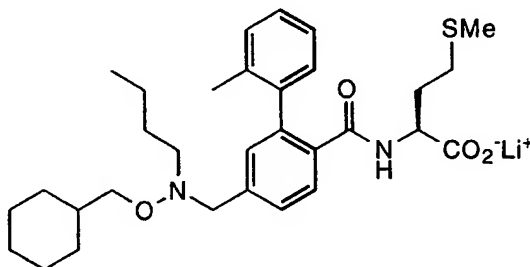
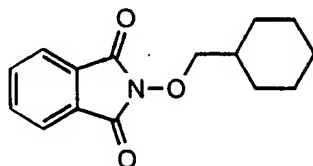
The desired product was prepared using the method described in Example 403H starting with the compound from Example 1184C and N-[4-Formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, prepared as in Example 403G. m/e (ESI)

14185

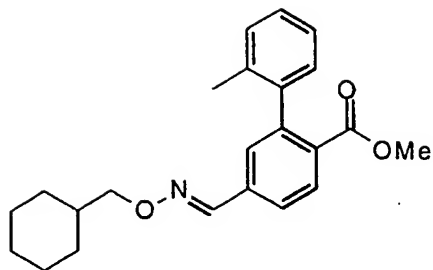
553 (MH⁻)

Example 1184EN-[4-N-(2-Cyclohexylethyl)-N-propyloxyaminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

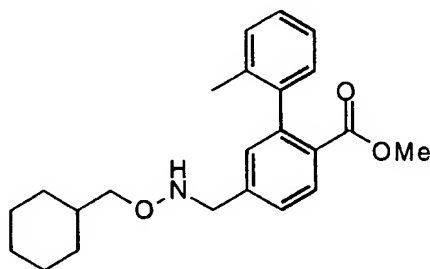
The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1184D. ¹H (300MHz, DMSO-d₆, δ) 7.53 (1H, d, J=9Hz), 7.38 (1H, dd, J=7&2Hz), 7.30-7.00 (5H, m), 6.92 (1H, m), 3.82 (2H, bs), 3.71 (1H, m), 3.41 (2H, m), 2.67 (2H, bt, J=8Hz), 2.25-1.95 (5H, m), 1.91 (3H, s), 1.90-1.50 (7H, m), 1.37 (5H, m), 1.15 (3H, m), 0.86 (2H, m), 0.76 (3H, t, J=8Hz). m/e (ESI) 539 (MH⁺) Anal.calc. for C₃₁H₄₃LiN₂O₄S·0.50 H₂O C 67.00, H 7.98, N 5.04 Found C 66.82, H 7.75, N 4.92

Example 1185Example 1185AN-Cyclohexylmethoxyphthalimide

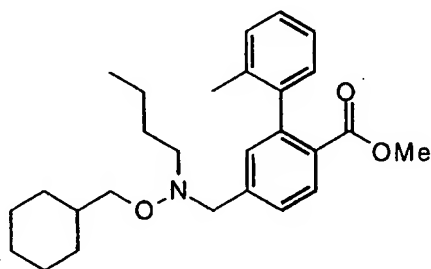
The desired product was prepared using the method described in Example 1176A starting with N-hydroxyphthalimide and cyclohexylmethanol.

Example 1185BN-(Cyclohexylmethyloxy)aminomethylidene-2-(2-methylphenyl)benzoic acid methyl ester

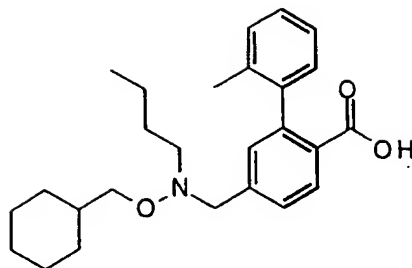
The desired product was prepared using the method described in Example 1176B starting with the compound from Example 1185A and N-[4-Formyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared using the method of Example 403G and starting with the alcohol prepared in Example 1178C.

Example 1185CN-(Cyclohexylmethyloxy)aminomethyl-2-(2-methylphenyl)benzoic acid methyl ester

The desired product was prepared using the method described in Example 1176C starting with the compound in Example 1185B. m/e (ESI) 368 (MH⁺)

Example 1185DN-[4-N--Butyl-N-(cyclohexylmethyloxy)aminomethyl]-2-(2-methylphenyl)benzoic acid methyl ester

The desired product was prepared using the method described in Example 1176D starting with the compound in Example 1185C. m/e (ESI) 424 (MH⁺)

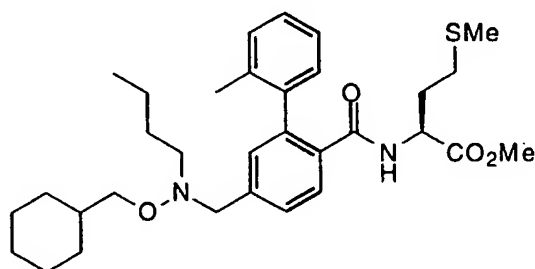


14230

Example 1185EN-[4-N--Butyl-N-(cyclohexylmethyloxy)aminomethyl]-2-(2-methylphenyl)benzoic acid

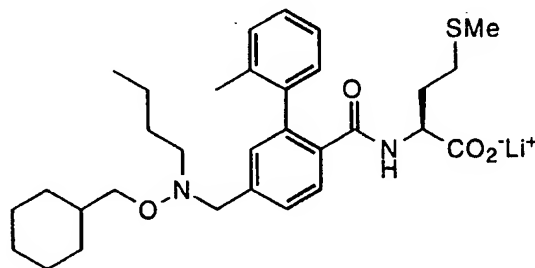
The desired product was prepared using the method described in Example 403E starting with the compound in Example 1185D.

14235

Example 1185FN-[4-N--Butyl-N-(cyclohexylmethyloxy)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

14240

The desired product was prepared using the method described in Example 403F starting with the compound in Example 1185E. m/e (ESI) 555 (MH⁺)

Example 1185GN-[4-N--Butyl-N-(cyclohexylmethyloxy)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

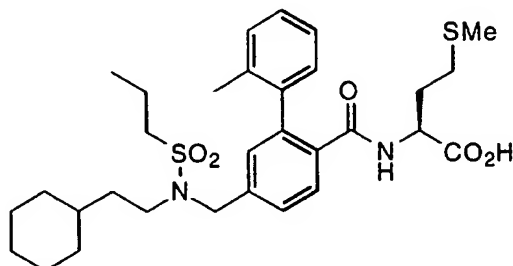
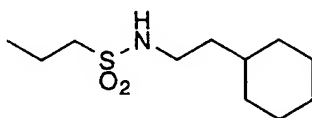
14245

The desired compound was prepared according to the method of Example 403I starting with the compound in Example 1185F. ¹H (300MHz, DMSO-d₆, δ) 7.51 (1H, d, J=9Hz), 7.37 (1H, bd), 7.30-7.05 (5H, m), 6.94 (1H, m), 3.82 (2H, bs), 3.68 (1H, m), 3.25 (2H, m), 2.64 (2H, t, J=8Hz), 2.25-1.95 (5H, m), 1.93 (3H, s), 1.90-1.40 (9H, m),

14250

1.31 (3H, m), 1.06 (3H, m), 0.85 (3H, t, J=8Hz), 0.73 (2H, m). m/e (ESI) 539 (MH⁺)
 Anal.calc. for C₃₁H₄₃LiN₂O₄S·2.00 H₂O C 63.90, H 8.13, N 4.81 Found C 63.63, H 7.68, N 4.62

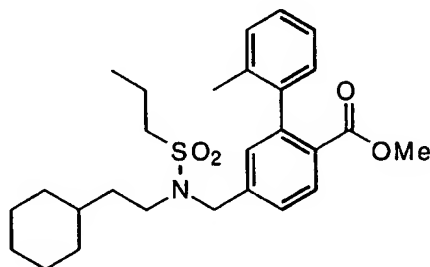
14255

Example 1187Example 1187A

14260

N-(2-Cyclohexylethyl)-N-propanesulfonylamine

The desired product was prepared using the method described in Example 1174A starting with cyclohexylethylamine and 1-propanesulfonyl chloride.

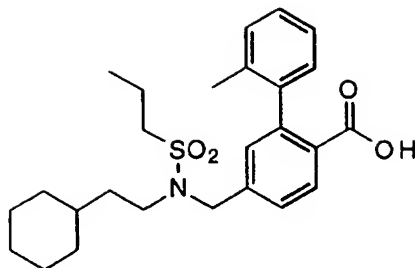


14265

Example 1187B4-(N-(2-Cyclohexylethyl)-N-propanesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester

The desired product was prepared using the method described in Example 1174B starting with N-(2-cyclohexylethyl)-N-propanesulfonylamine, prepared as in Example 1187A, and 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as in Example 1178A-D. m/e (ESI) 472 (MH⁺)

14270

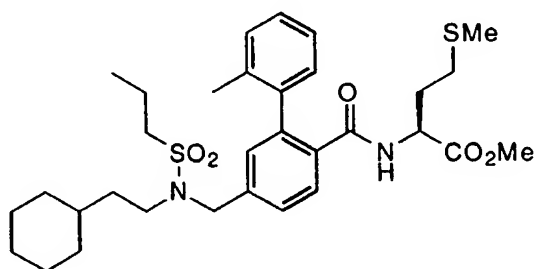


14275

Example 1187C

4-(N-(2-Cyclohexylethyl)-N-propanesulfonylaminomethyl)-2-(2-methylphenyl)benzoic acid

The desired acid was prepared using the method described in Example 403E starting with the product from Example 1187B.



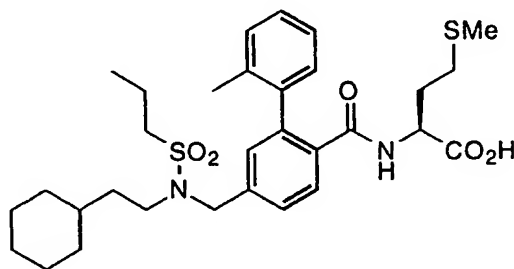
14280

Example 1187D

N-[4-N-(2-Cyclohexylethyl)-N-propanesulfonylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired compound was prepared using the method described in Example 403F starting with the product from Example 1187C. m/e (ESI) 601 (MH⁺)

14285

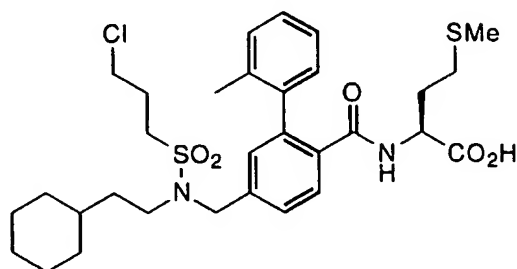
Example 1187E

N-[4-N-(2-Cyclohexylethyl)-N-propanesulfonylaminomethyl]-2-(2-methylphenyl)benzoyl]methionine

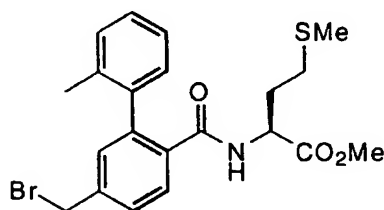
14290

The desired compound was prepared according to the method of Example 403I starting with the compound prepared in Example 1187D. ¹H (300MHz, CDCl₃, δ) 8.00 (1H, dd, J=8&7Hz), 7.43 (1H, dd, J=7&2Hz), 7.40-7.10 (5H, m), 5.90 (1H, m), 4.58 (1H, m), 4.42 (2H, s), 3.20 (2H, m), 2.94 (2H, m), 2.20-2.00 (7H, m), 2.00-1.80 (4H,

14295 m), 1.60 (6H, m), 1.38 (2H, m), 1.15 (4H, m), 1.05 (3H, t, J=8Hz), 0.86 (2H, m). m/e
(ESI) 587 (MH⁺) Anal. calc. for C₃₁H₄₄N₂O₅S₂·0.25 H₂O C 62.75, H 7.56, N 4.72
Found C 62.75, H 7.56, N 4.49

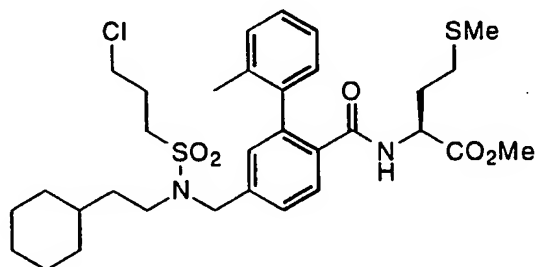


14300

Example 1188Example 1188A

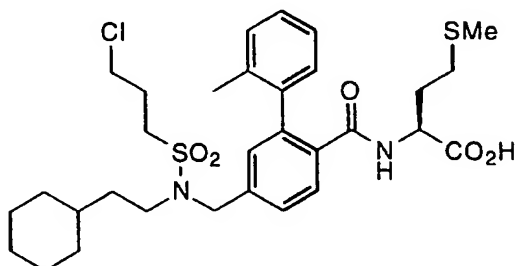
14305 N-[Bromomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

To a stirred solution at -10°C under N₂ of N-[4-hydroxymethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester (200 mg, 0.517 mmol), prepared as in Example 403F, and carbon tetrabromide (189 mg, 0.568 mmol) in CH₂Cl₂ (5 mL) was added triphenylphosphine (163 mg, 0.620 mmol). Reaction stirred one hour at -10°C, and
14310 then, solvents concentrated in vacuo to produce a colorless glass. The residue could not be stored, and so, was used directly in the reaction in Example 1188B.

Example 1188B

14315 N-[4-N-(3-Chloropropanesulfonyl)-N-(2-cyclohexylethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

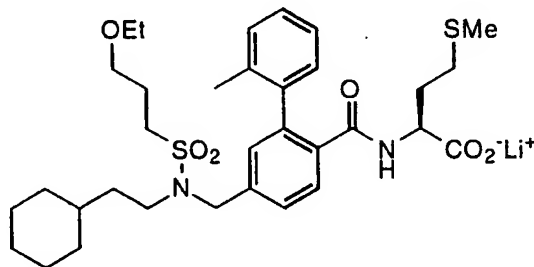
The desired compound was prepared using the method described in Example 1174B (except reaction run at -40°C) starting with the product from Example 1188A and N-(3-chloropropanesulfonyl)-N-(2-cyclohexylethyl)amine, prepared as in Example 1189A using the method described in Example 1174A. m/e (ESI) 635 (MH^+)



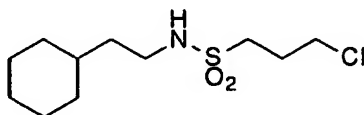
Example 1188C

N-[4-N-(3-Chloropropanesulfonyl)-N-(2-cyclohexylethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1188B. ^1H (300MHz, CDCl_3 , δ) 8.01 (1H, bt, $J=8\text{Hz}$), 7.46 (1H, dd, $J=7\&2\text{Hz}$), 7.40-7.10 (5H, m), 5.90 (1H, m), 4.59 (1H, m), 4.45 (2H, s), 3.68 (2H, t, $J=8\text{Hz}$), 3.22 (2H, bt, $J=7\text{Hz}$), 3.12 (2H, t, $J=8\text{Hz}$), 2.31 (2H, m), 2.20-2.05 (4H, m), 2.03 (3H, s), 1.92 (2H, m), 1.60 (6H, m), 1.40 (2H, m), 1.30-1.00 (4H, m), 0.85 (2H, m). m/e (ESI) 621 (MH^+) Anal. calc. for $\text{C}_{31}\text{H}_{43}\text{Cl}_1\text{N}_2\text{O}_5\text{S}_2 \cdot 0.50 \text{H}_2\text{O}$ C 58.89, H 7.01, N 4.43 Found C 58.96, H 7.04, N 4.40



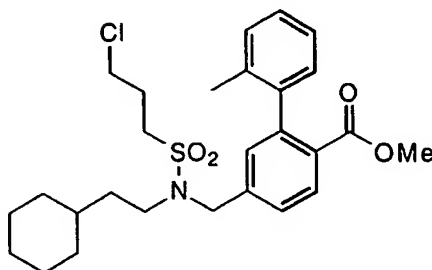
Example 1189



Example 1189A

N-(3-Chloropropanesulfonyl)-N-(2-cyclohexylethyl)amine

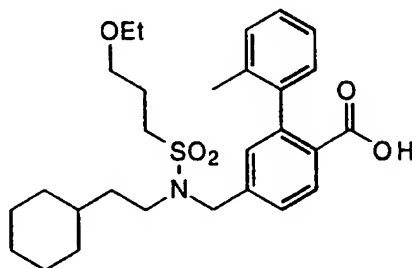
14340 The desired compound was prepared using the method described in Example 1174A starting with cyclohexylethylamine and 3-chloropropanesulfonyl chloride.



Example 1189B

14345 4-N-(3-Chloropropanesulfonyl)-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoic acid methyl ester

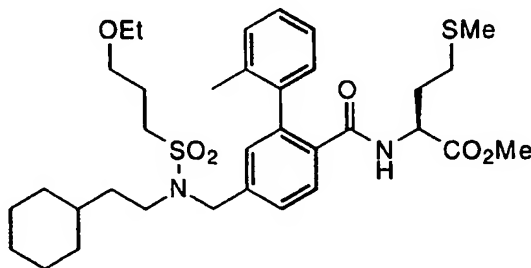
The desired product was prepared using the method described in Example 1174B starting with the compound from Example 1189A and 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as in Example 1178A-D. m/e (ESI) 506 (MH⁺)



Example 1189C

14355 N-[4-N-(2-Cyclohexylethyl)-N-(3-ethoxypropanesulfonyl)aminomethyl]-2-(2-methylphenyl)benzoic acid

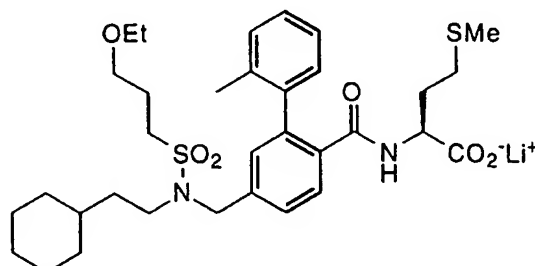
The acid was prepared using the method described in Example 403E starting with the product from Example 1189B. Chloride was displaced by ethoxide ion.



Example 1189D

N-[4-N-(2-Cyclohexylethyl)-N-(3-ethoxypropanesulfonyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

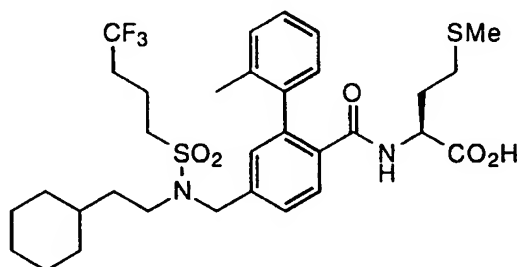
The compound was prepared using the method described in Example 403F starting with the product from Example 1189C. m/e (ESI) 645 (MH⁻)



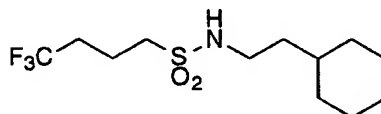
Example 1189E

N-[4-N-(2-Cyclohexylethyl)-N-(3-ethoxypropanesulfonyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1189D. ¹H (300MHz, DMSO-d₆, δ) 7.54 (1H, d, J=8Hz), 7.41 (1H, dd, J=7&2Hz), 7.30-7.10 (5H, m), 6.97 (1H, d, J=7Hz), 4.42 (2H, bs), 3.68 (1H, m), 3.43 (2H, q, J=7Hz), 3.40 (2H, m), 3.16 (4H, m), 2.20-1.95 (5H, m), 1.95 (3H, s), 1.90-1.65 (3H, m), 1.55 (6H, m), 1.27 (2H, m), 1.10 (7H, bt, J=8Hz), 0.78 (2H, m). m/e (ESI) 631 (MH⁻) Anal.calc. for C₃₃H₄₇LiN₂O₆S₂·0.50 H₂O C 61.18, H 7.47, N 4.32 Found C 61.15, H 7.53, N 4.15



Example 1190

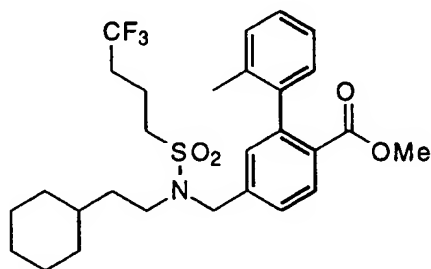


Example 1190A

N-(2-Cyclohexylethyl)-N-(3-trifluoromethylpropanesulfonyl)amine

- 14385 To a stirred solution at 0°C under N₂ of 4,4,4-trifluoro-1-bromobutane (2.00 g, 10.5 mmol) in anhydrous DMF (10 mL) was added dropwise a slurry of t-butanethiol sodium salt (1.29 g, 11.5 mmol) in anhydrous DMF (25 mL) such that the temperature was maintained below 5°C. Mixture stirred one hour at 0°C, and then, diluted with water and extracted with ether. Extracts dried with Na₂SO₄, filtered, and concentrated in vacuo.
- 14390 Residue dissolved in 1:1 water/EtOH at 0°C, and to this was bubbled in chlorine gas for 45 minutes. After the chlorine addition, N₂ was bubbled into the black-green mixture until the green color disappeared (30 minutes). The mixture was made a more homogeneous solution by addition of CH₂Cl₂, and to this was added carefully an aqueous 2M Na₂CO₃ solution until mixture was basic (pH 10). Cyclohexylethylamine (1.14 g, 9.00 mmol) was added, and this two-phase solution was stirred at room temperature overnight. Reaction diluted with water and extracted with CHCl₃ (2x). Extracts dried with Na₂SO₄, filtered, and concentrated. Residue purified by flash chromatography on silica gel eluting with 20% EtOAc/Hexanes to afford the desired product as a light brown oil (1.02 g, 32%). m/e (DCI) 319 (MH+NH₃⁺)

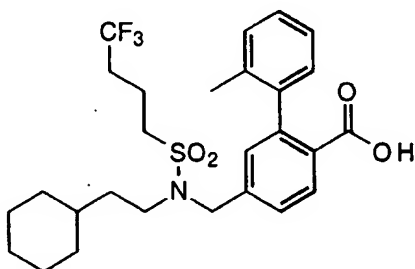
14400



Example 1190B

4-(N-(2-Cyclohexylethyl)-N-(3-trifluoromethylpropanesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester

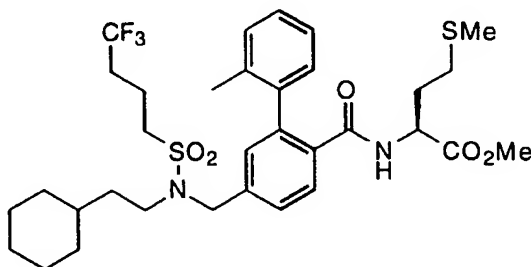
- 14405 The desired product was prepared using the method described in Example 1174B starting with N-(2-cyclohexylethyl)-N-(3-trifluoromethylpropanesulfonyl)amine, prepared as in Example 1190A, and 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as in Example 1178A-D.



14410

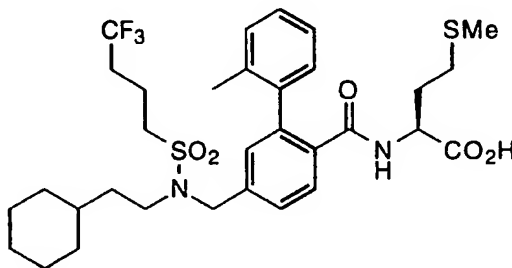
Example 1190C4-(N-(2-Cyclohexylethyl)-N-(3-trifluoromethylpropanesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoic acid

The desired acid was prepared using the method described in Example 403E starting
 14415 with the product from Example 1190B. m/e (ESI) 524 (MH⁻)

Example 1190DN-[4-N-(2-Cyclohexylethyl)-N-(3-trifluoromethylpropanesulfonyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

14420

The desired compound was prepared using the method described in Example 403F
 starting with the product from Example 1190C. m/e (ESI) 669 (MH⁻)

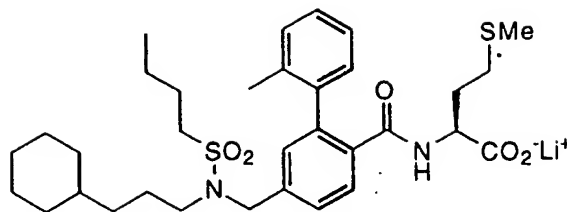


14425

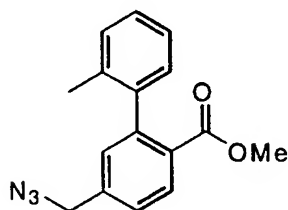
Example 1190EN-[4-N-(2-Cyclohexylethyl)-N-(3-trifluoromethylpropanesulfonyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I
 starting with the compound in Example 1190D. ¹H (300MHz, CDCl₃, δ) (rotamer)
 14430 8.01(7.98) (1H, d, J=8Hz), 7.46 (1H, dd, J=7&2Hz), 7.40-7.10 (5H, m), 5.92 (1H, m),
 4.80 (1H, bs), 4.58 (1H, m), 4.45 (2H, s), 3.22 (2H, bt, J=7Hz), 3.03 (2H, t, J=8Hz),
 2.30 (2H, m), 2.20-2.00 (10H, m), 1.92 (1H, m), 1.62 (6H, m), 1.40 (2H, m), 1.30-1.00
 (4H, m), 0.87 (2H, m). m/e (ESI) 655 (MH⁻) Anal.calc. for C₃₂H₄₃F₃N₂O₅S₂ C 58.52,
 H 6.60, N 4.26 Found C 58.27, H 6.63, N 4.13

14435

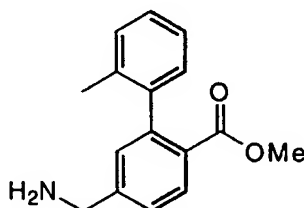
Example 1191

14440

Example 1191A4-Azidomethyl-2-(2-methylphenyl)benzoic acid methyl ester

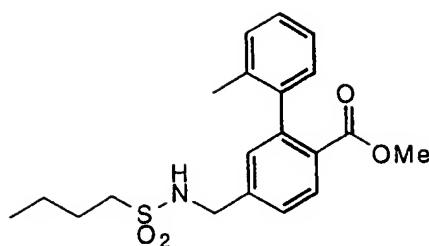
14445 To a stirred mixture at 0°C under N₂ of sodium azide (1.47 g, 22.6 mmol) in anhydrous DMF (30 mL) was added a solution of 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester (6.00 g, 18.8 mmol), prepared as in Example 1178A-D, in anhydrous DMF (10 mL). Reaction stirred overnight at room temperature. Reaction diluted with EtOAc and washed with water and brine. Organic layer dried with Na₂SO₄, filtered, and concentrated in vacuo.

14450

Example 1191B4-Aminomethyl-2-(2-methylphenyl)benzoic acid methyl ester

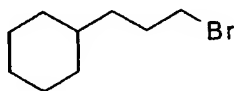
14455 To a flask at ambient temperature under N₂ containing 10% palladium on carbon catalyst (1.0 g) was added a solution of 4-azidomethyl-2-(2-methylphenyl)benzoic acid methyl ester (5.00 g, 17.8 mmol), prepared as in Example 1191A, in MeOH (75 mL). Two drops of conc. HCl added, and reaction stirred vigorously overnight under an atmosphere of H₂. Catalyst filtered off through celite and washed with MeOH. Filtrate concentrated in vacuo, and residue taken up in an aqueous 4N NaOH solution. Aqueous solution extracted with CHCl₃ (3x), and extracts dried with Na₂SO₄, filtered, and concentrated in vacuo to afford the desired product (1.37 g, 30%). m/e (DCI) 256 (MH⁺)

14460

Example 1191C

14465 4-N-Butanesulfonylaminomethyl-2-(2-methylphenyl)benzoic acid methyl ester

The desired compound was prepared using the method described in Example 1174A starting with 4-aminomethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as in Example 1191B, and butanesulfonyl chloride. m/e (ESI) 374 (MH⁻)

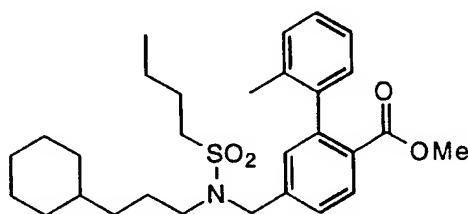


14470

Example 1191D1-Bromo-3-cyclohexylpropane

The desired compound was prepared according to the method of Example 1178D starting with 3-cyclohexyl-1-propanol. ¹H (300MHz, CDCl₃, δ) 3.40 (2H, t, J=8Hz),

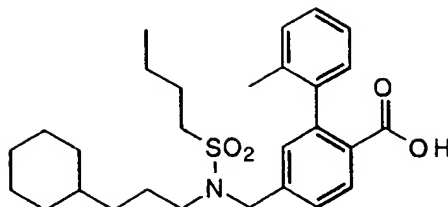
14475 1.85 (2H, m), 1.80-1.50 (6H, m), 1.40-1.10 (5H, m), 0.90 (2H, m).

Example 1191E

N-[4-N-(Butanesulfonyl)-N-(3-cyclohexylpropyl)aminomethyl-2-(2-methylphenyl)benzoic acid methyl ester

14480

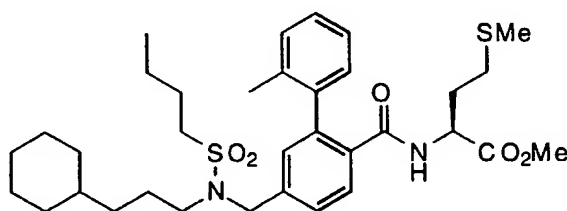
The desired compound was prepared using the method described in Example 1174B starting with the compounds from Example 1191C and Example 1191D. m/e (ESI) 500 (MH⁺)



Example 1191F

N-[4-N-(Butanesulfonyl)-N-(3-cyclohexylpropyl)aminomethyl]-2-(2-methylphenyl)benzoic acid

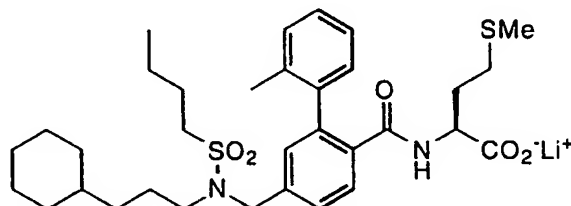
The acid was prepared using the method described in Example 403E starting with the compound from Example 1191E.



Example 1191G

N-[4-N-(Butanesulfonyl)-N-(3-cyclohexylpropyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

The compound was prepared using the method described in Example 403F starting with the compound from Example 1191F. m/e (ESI) 629 (MH⁻)

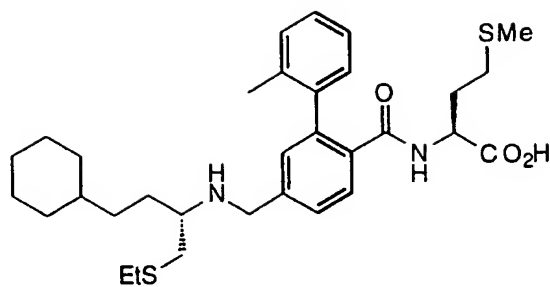
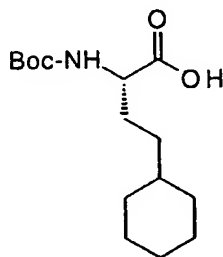


Example 1191H

N-[4-N-(Butanesulfonyl)-N-(3-cyclohexylpropyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1191G. ¹H (300MHz, DMSO-d₆, δ) 7.54 (1H, d, J=8Hz), 7.41 (1H, bd, J=7Hz), 7.30-7.05 (5H, m), 6.97 (1H, d, J=7Hz), 4.42 (2H, s), 3.68 (1H, m), 3.10 (4H, bt, J=7Hz), 2.20-1.95 (5H, m), 1.91 (3H, s), 1.90-1.45 (9H, m), 1.45-1.20 (4H, m), 1.20-0.90 (6H, m), 0.88 (3H, t, J=8Hz), 0.73 (2H, m). m/e (ESI) 615 (MH⁻) Anal. calc. for C₃₃H₄₇LiN₂O₅S₂·0.75 H₂O C 62.29, H 7.68, N 4.40 Found C 62.18, H 7.75, N 4.36

14510

Example 1193

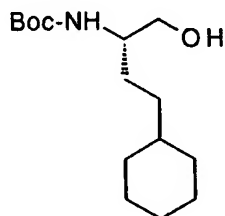
14515

Example 1193A(2S)-t-Butoxycarbonylamino-4-cyclohexylbutanoic acid

To a solution of Boc-homophenylalanine (3.00 g, 10.8 mmol) in CH_2Cl_2 at room temperature was added a solution of 4N HCl in dioxane (20 mL, 80 mmol), and mixture stirred overnight. Solvents concentrated, and white powder that resulted was reduced under high pressure (4 atm. H_2) using platinum/HCl. The white solid that resulted from the reduction was mixed with aqueous 4N NaOH (30 mL), water (30 mL), and THF (50 mL) at room temperature, and to this was added di-t-butyl dicarbonate (3.5 g, 16 mmol). Reaction heated at 70°C overnight. Reaction cooled to 0°C , and an aqueous solution of 3N HCl added until the pH reached 6. Product extracted out with CHCl_3 , and extracts dried with Na_2SO_4 , filtered, and concentrated in vacuo to produce a white solid (3.24 g, 106%). m/e (DCI) 286 (MH^+)

14520

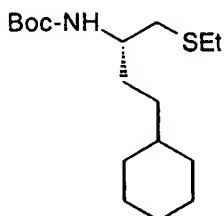
14525



14530

Example 1193B(2S)-t-Butoxycarbonylamino-4-cyclohexylbutan-1-ol

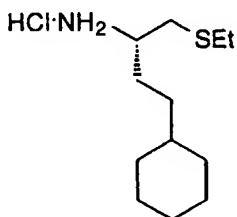
To a solution at -5°C under N₂ of (2S)-t-butoxycarbonylamino-4-cyclohexylbutanoic acid (3.24 g, 10.8 mmol), prepared as in Example 1193A, in anhydrous THF (20 mL) was added dropwise a 1.0M borane-THF complex (32.3 mL, 32.3 mmol) in THF. After addition, reaction stirred overnight at room temperature. Reaction cooled to 0°C and quenched with an aqueous 4N NaOH solution. Stirred 30 minutes at room temperature, and then, extracted with CH₂Cl₂ (3x). Extracts dried with Na₂SO₄, filtered, and concentrated in vacuo. Residue purified by flash chromatography on silica gel eluting with 30% EtOAc/Hexanes to afford the desired product as a colorless oil (696 mg, 23%). m/e (DCI) 272 (MH⁺)



Example 1193C

(2S)-t-Butoxycarbonylamino-4-cyclohexyl-1-ethylthiobutane

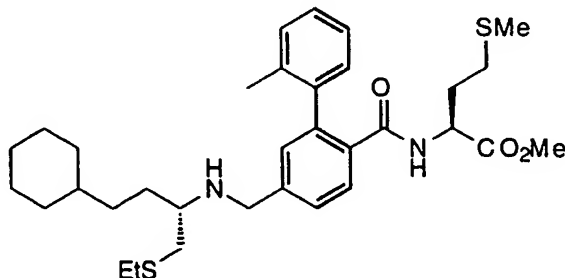
The desired compound was prepared using the method described in Example 403B and 403C starting with the product from Example 1193B. m/e (DCI) 316 (MH⁺)



Example 1193D

(2S)-Amino-4-cyclohexyl-1-ethylthiobutane hydrochloride salt

The desired compound was prepared using the method described in Example 403D starting with the product from Example 1193C.

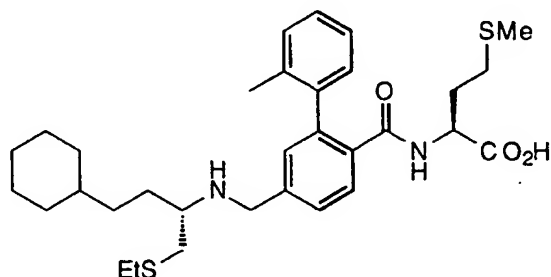


14555

Example 1193E

N-[4-N-(4-Cyclohexyl-1-ethylthiobutan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired compound was prepared using the method described in Example 403H starting with the product from Example 1193D and N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, prepared as in Example 403G. m/e (ESI) 585 (MH⁺)

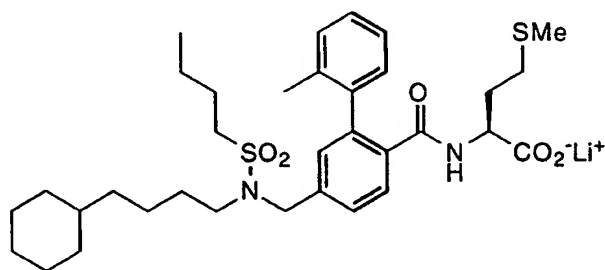
Example 1193F

14565

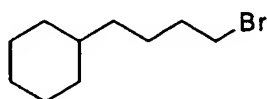
N-[4-N-(4-Cyclohexyl-1-ethylthiobutan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1193E. ¹H (300MHz, CDCl₃, δ) 7.72 (1H, m), 7.45 (1H, m), 7.40-7.00 (5H, m), 6.18 (1H, m), 4.36 (1H, m), 4.00 (2H, m), 2.95 (1H, m), 2.82 (1H, m), 2.73 (1H, m), 2.44 (2H, m), 2.20-2.00 (7H, m), 1.98 (3H, bs), 1.90-1.40 (7H, m), 1.20 (9H, t, J=8Hz), 0.87 (3H, m). m/e (ESI) 569 (MH⁻) Anal.calc. for C₃₂H₄₆N₂O₃S₂·0.75 H₂O C 65.77, H 8.19, N 4.79 Found C 65.74, H 8.08, N 4.69

14570



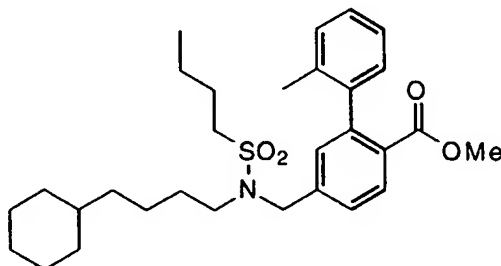
14575

Example 1194Example 1194A

14580

1-Bromo-4-cyclohexylbutane

The desired compound was prepared according to the method of Example 1178D starting with 4-cyclohexyl-1-butanol. ^1H (300MHz, CDCl_3 , δ) 3.40 (2H, t, $J=8\text{Hz}$), 1.83 (2H, m), 1.80-1.50 (6H, m), 1.42 (2H, m), 1.30-1.10 (5H, m), 0.85 (2H, m).

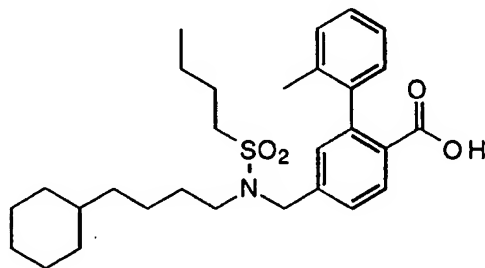


14585

Example 1194B

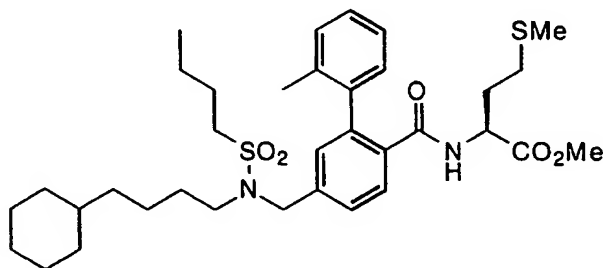
4-N-(Butanesulfonyl)-N-(4-cyclohexylbutyl)aminomethyl-2-(2-methylphenyl)benzoic acid
methyl ester

The desired compound was prepared using the method described in Example 1174B starting with the compounds from Example 1191C and Example 1194A. m/e (ESI) 514 (MH^+)

Example 1194C

4-N-(Butanesulfonyl)-N-(4-cyclohexylbutyl)aminomethyl-2-(2-methylphenyl)benzoic acid

The acid was prepared using the method described in Example 403E starting with the compound from Example 1194B.

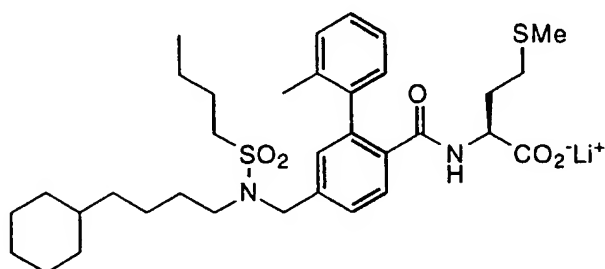


14600

Example 1194D

N-[4-N-(Butanesulfonyl)-N-(4-cyclohexylbutyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

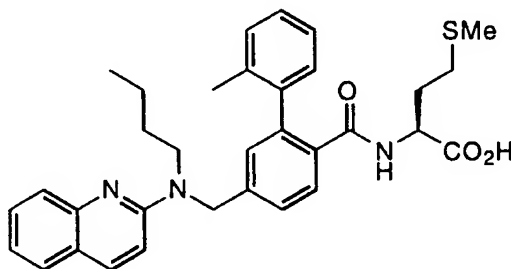
The compound was prepared using the method described in Example 403F starting with the compound from Example 1194C. ¹H (300MHz, CDCl₃, δ) 7.96 (1H, m), 7.43 (1H, dd, J=7&2Hz), 7.40-7.10 (5H, m), 5.90 (1H, bd, J=7Hz), 4.62 (1H, m), 4.44 (2H, s), 3.64 (3H, s), 3.18 (2H, m), 2.96 (2H, m), 2.20-1.85 (8H, m), 1.75-1.50 (9H, m), 1.50-1.30 (4H, m), 1.25-1.00 (8H, m), 0.94 (3H, t, J=8Hz), 0.82 (2H, m).



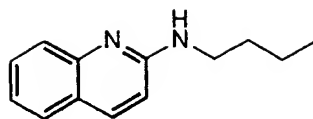
Example 1194E

N-[4-N-(Butanesulfonyl)-N-(4-cyclohexylbutyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1194D. ¹H (300MHz, DMSO-d₆, δ) 7.56 (1H, d, J=8Hz), 7.41 (1H, dd, J=7&2Hz), 7.30-7.05 (5H, m), 6.98 (1H, d, J=7Hz), 4.42 (2H, bs), 3.68 (1H, m), 3.13 (4H, m), 2.20-1.95 (5H, m), 1.92 (3H, s), 1.90-1.45 (9H, m), 1.45-1.20 (4H, m), 1.20-0.90 (8H, m), 0.88 (3H, t, J=8Hz), 0.78 (2H, m). m/e (ESI) 629 (MH⁺) Anal.calc. for C₃₄H₄₉LiN₂O₅S₂·0.75 H₂O C 62.79, H 7.83, N 4.31 Found C 62.69, H 7.84, N 4.24

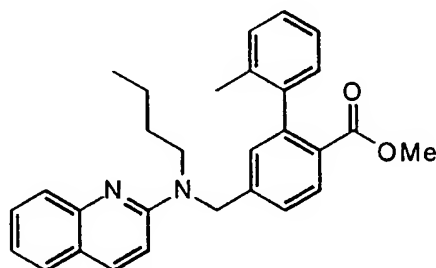


Example 1195

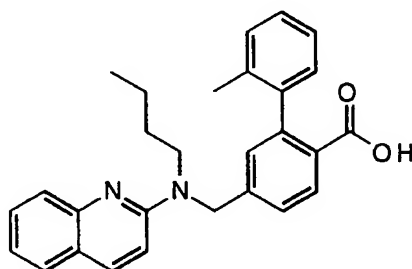
Example 1195AN-Butyl-N-quinolin-2-ylamine

14630 2-Chloroquinoline (500 mg, 3.06 mmol), butylamine (0.90 mL, 9.16 mmol), and diisopropylethylamine (0.82 mL, 4.58 mmol) were dissolved in acetonitrile (5 mL), and solution refluxed 2 days. Reaction cooled and diluted with EtOAc. Reaction washed with water and brine. Organic layer dried with Na₂SO₄, filtered, and concentrated in vacuo. Residue purified by flash chromatography on silica gel eluting with 15% EtOAc/Hexanes to afford the desired product as a pale yellow oil (188 mg, 31%). m/e (DCI) 201 (MH⁺)

14635

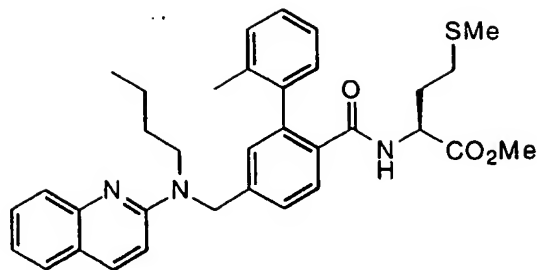
Example 1195B4-N-Butyl-N-quinolin-2-ylaminomethyl-2-(2-methylphenyl)benzoic acid methyl ester

14640 The desired compound was prepared according to the method of Example 1174B starting with 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as in Example 1178A-D, and the compound from Example 1195A.

Example 1195C4-N-Butyl-N-quinolin-2-ylaminomethyl-2-(2-methylphenyl)benzoic acid

14645

The desired acid was prepared using the method described in Example 403E starting with the product from Example 1195B.



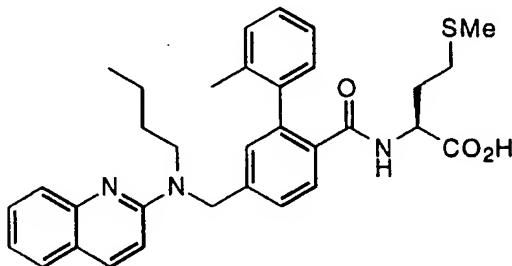
14650

Example 1195D

N-[4-N-Butyl-N-quinolin-2-ylaminomethyl]-2-(2-methylphenyl)benzoyl-methionine methyl ester

The desired compound was prepared using the method described in Example 403F starting with the product from Example 1195C. m/e (ESI) 570 (MH⁺)

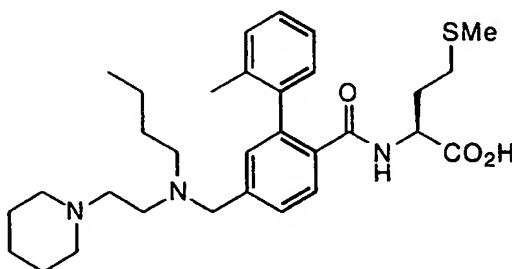
14655

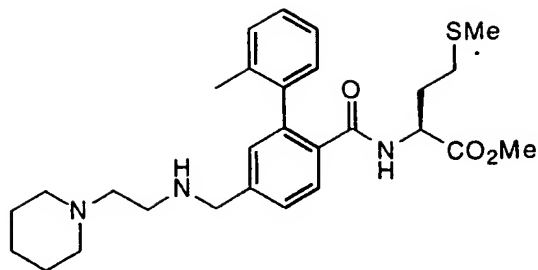
Example 1195E

N-[4-N-Butyl-N-quinolin-2-ylaminomethyl]-2-(2-methylphenyl)benzoyl-methionine

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1195D. ¹H (300MHz, CDCl₃, δ) 7.95-7.80 (3H, m), 7.72 (1H, m), 7.60-7.40 (2H, m), 7.37 (1H, dd, J=7&2Hz), 7.30-7.00 (5H, m), 6.84 (1H, d, J=9Hz), 6.03 (1H, m), 5.03 (2H, bs), 4.44 (1H, m), 3.62 (2H, m), 2.20-2.00 (5H, m), 1.96 (3H, s), 1.85 (1H, m), 1.65 (2H, m), 1.51 (1H, m), 1.37 (2H, m), 0.93 (3H, t, J=8Hz). m/e (ESI) 554 (MH⁺) Anal.calc. for C₃₃H₃₇N₃O₃S·0.40 H₂O C 70.41, H 6.77, N 7.46 Found C 70.62, H 6.68, N 7.07

14665

Example 1196

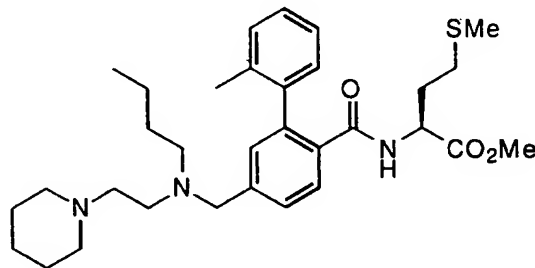


14670

Example 1196A

N-[4-(N-(2-piperidin-1-ylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

14675 The desired compound was prepared using the method described in Example 403H starting with N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, prepared as in Example 403G, and 1-(2-aminoethyl)piperidine. m/e (ESI) 498 (MH⁺)

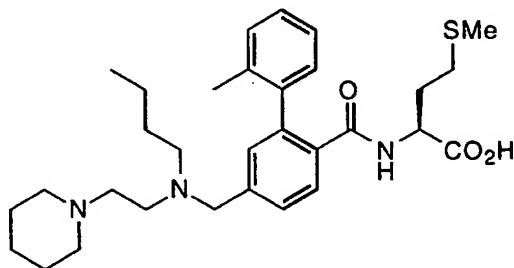
Example 1196B

14680

N-[4-(N-Butyl-N-(2-piperidin-1-ylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

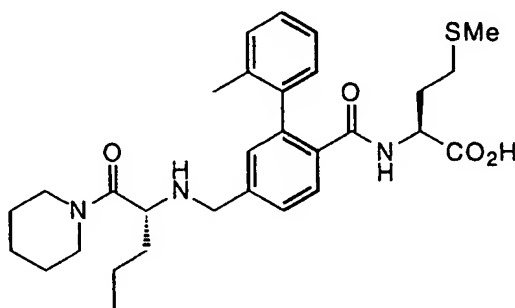
The desired compound was prepared using the method described in Example 403H starting with the compound prepared in Example 1196A and butyraldehyde. m/e (ESI) 552 (MH⁺)

14685

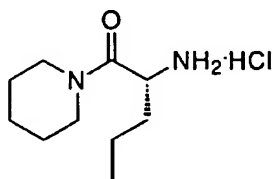
Example 1196C

N-[4-(N-Butyl-N-(2-piperidin-1-ylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

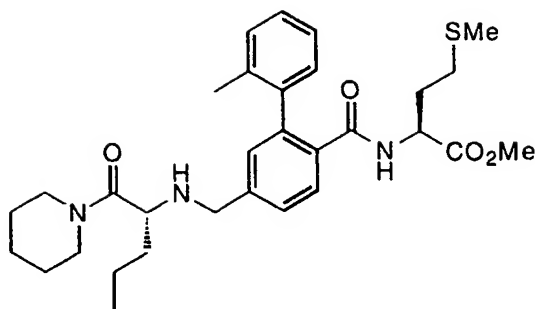
14690 The desired compound was prepared according to the method of Example 4031
 starting with the compound from Example 1196B. ^1H (300MHz, CDCl_3 , δ) 7.62 (1H, d, $J=8\text{Hz}$), 7.30-7.10 (5H, m), 7.09 (1H, bs), 6.42 (1H, m), 4.35 (1H, m), 3.63 (2H, m),
 3.05-2.75 (8H, m), 2.42 (2H, bt, $J=7\text{Hz}$), 2.20-1.90 (9H, m), 1.90-1.60 (5H, m), 1.55
 14695 (2H, m), 1.40 (2H, m), 1.22 (2H, m), 0.83 (3H, t, $J=8\text{Hz}$). m/e (ESI) 538 (MH^+)
 Anal. calc. for $\text{C}_{31}\text{H}_{45}\text{N}_3\text{O}_3\text{S}\cdot 0.75\text{H}_2\text{O}$ C 67.30, H 8.47, N 7.59 Found C 67.21, H
 8.39, N 7.52



14700

Example 1197Example 1197AN-(1-Morpholinocarbonyl)butylamine hydrochloride salt

14705 To a stirred solution at room temperature of Boc-L-norvaline (500 mg, 2.30 mmol)
 and piperidine (0.27 mL, 2.76 mmol) in DMF (5 mL) was added 1-ethyl-3-(3-
 dimethylaminopropyl)carbodiimide (530 mg, 2.76 mmol). Reaction stirred overnight at
 room temperature. Reaction diluted with EtOAc and washed with water and brine. Organic
 layer dried with Na_2SO_4 , filtered, and concentrated in vacuo. Residue mixed with a 4N
 14710 HCl solution (10 mL, 40 mmol) in dioxane at room temperature overnight. Solvents
 concentrated in vacuo to afford the desired compound (222 mg, 44%). m/e (DCI) 185
 (MH^+)



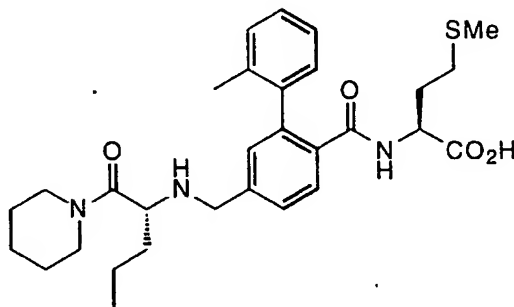
14715

Example 1197BN-[4-N-((1-Morpholinocarbonyl)butyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired compound was prepared using the method described in Example 403H starting with N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, prepared as

14720

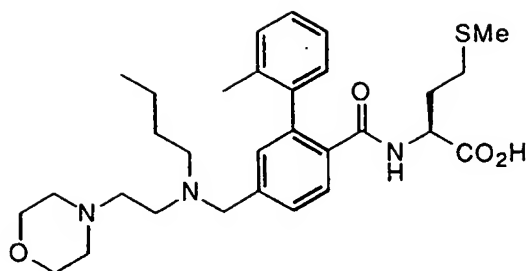
in Example 403G, and the compound prepared in Example 1197A. m/e (ESI) 554 (MH⁺)

Example 1197CN-[4-N-((1-Morpholinocarbonyl)butyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

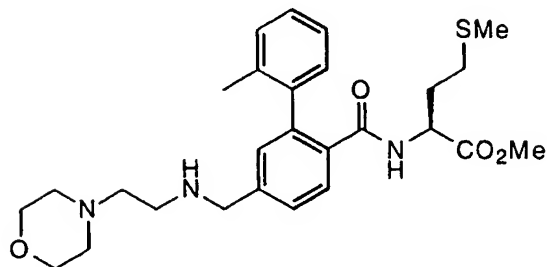
14725

The desired compound was prepared using the method described in Example 403I starting with the compound from Example 1197B. ¹H (300MHz, CDCl₃, δ) 7.82 (1H, m), 7.43 (1H, dd, J=7&2Hz), 7.40-7.20 (4H, m), 7.17 (1H, d, J=2Hz), 6.08 (1H, m), 5.97 (1H, m), 4.43 (1H, m), 4.20-3.80 (2H, m), 3.69 (2H, m), 3.60-3.30 (3H, m), 2.20-1.90 (8H, m), 1.91 (2H, m), 1.66 (4H, m), 1.57 (4H, m), 1.30 (2H, m), 0.89 (3H, t, J=8Hz). m/e (ESI) 538 (MH⁺) Anal.calc. for C₃₀H₄₁N₃O₄S·0.75 H₂O C 65.13, H 7.74, N 7.59 Found C 65.40, H 7.44, N 7.26

14730



14735

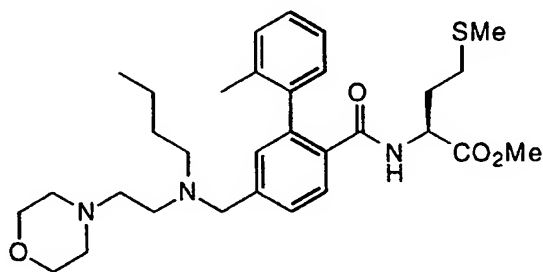
Example 1198Example 1198A

14740

N-[4-(N-(2-Morpholin-4-ylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired compound was prepared using the method described in Example 403H starting with N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, prepared as in Example 403G, and 4-(2-aminoethyl)morpholine. m/e (ESI) 500 (MH⁺)

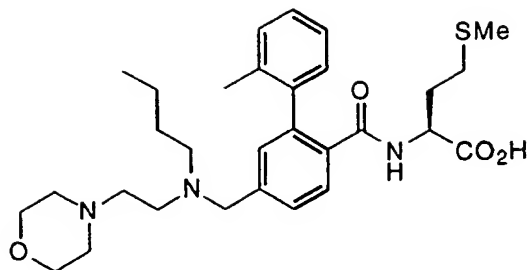
14745

Example 1198B

N-[4-N-Butyl-N-(2-morpholin-4-ylethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

14750

The desired compound was prepared using the method described in Example 403H starting with the compound prepared in Example 1198A and butyraldehyde. m/e (ESI) 554 (MH⁺)

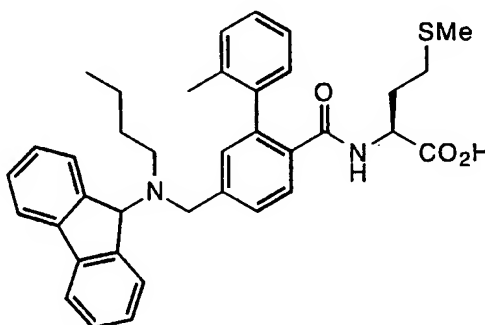
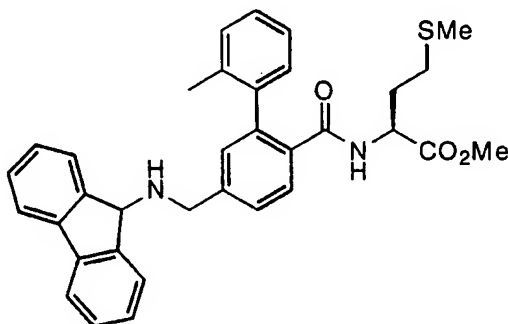


14755

Example 1198CN-[4-N-Butyl-N-(2-morpholin-4-ylethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1198B. ¹H (300MHz, CDCl₃, δ) 7.71 (1H, d, J=9Hz), 7.43 (1H, bd, J=8Hz), 7.30-7.10 (5H, m), 6.25 (1H, m), 4.39 (1H, m), 3.83 (2H, bs), 3.72 (4H, m), 2.89 (2H, m), 2.80-2.50 (8H, m), 2.20-1.80 (9H, m), 1.62 (1H, m), 1.50 (2H, m), 1.27 (2H, m), 0.88 (3H, t, J=8Hz). m/e (ESI) 540 (MH⁺) Anal. calc. for C₃₀H₄₃N₃O₄S·0.50 H₂O C 65.42, H 8.05, N 7.63 Found C 65.22, H 7.92, N 7.47

14765

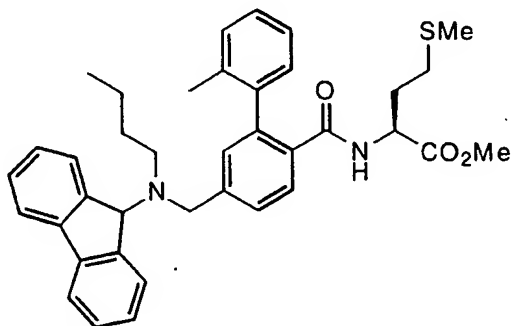
Example 1199

14770

Example 1199AN-[4-(N-(Fluoren-9-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired compound was prepared using the method described in Example 403H starting with N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, prepared as in Example 403G, and 9-aminofluorene hydrochloride salt m/e (ESI) 551 (MH⁺)

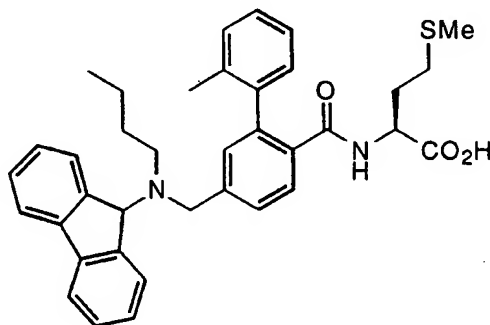
14775

Example 1199B

N-[4-N-Butyl-N-(fluoren-9-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

14780

The desired compound was prepared using the method described in Example 403H starting with the compound prepared in Example 1199A and butyraldehyde. m/e (ESI) 605 (MH⁻)



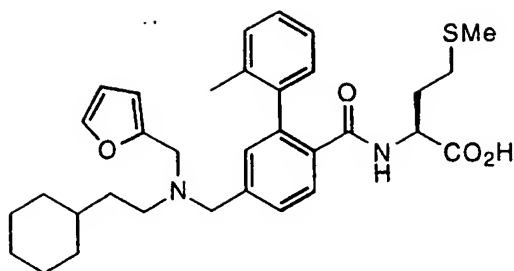
14785

Example 1199C

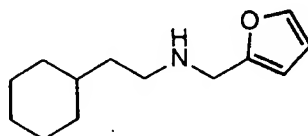
N-[4-N-Butyl-N-(fluoren-9-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

14790

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1199B. ¹H (300MHz, CDCl₃, δ) 7.91 (1H, m), 7.67 (3H, m), 7.47 (1H, bd, J=8Hz), 7.40-7.10 (10H, m), 5.84 (1H, m), 5.00 (1H, bs), 4.52 (1H, m), 3.53 (2H, bs), 2.64 (2H, m), 2.20-1.95 (8H, m), 1.90 (1H, m), 1.52 (3H, m), 1.32 (2H, m), 0.83 (3H, bt, J=8Hz). m/e (ESI) 591 (MH⁻) Anal.calc. for C₃₇H₄₀N₂O₃S·0.50 H₂O C 73.85, H 6.87, N 4.65 Found C 74.07, H 6.70, N 4.63



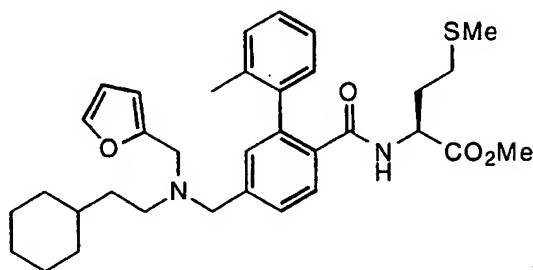
14795

Example 1200

14800

Example 1200AN-(2-Cyclohexylethyl)-N-(furan-2-ylmethyl)amine

The desired amine was prepared using the method described in Example 1171A starting with cyclohexylethylamine and 2-furoic acid. m/e (DCI/NH₃) 208 (MH⁺)



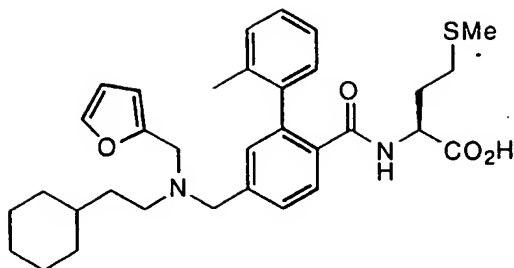
14805

Example 1200B

N-[4-N-(2-Cyclohexylethyl)-N-(furan-2-ylmethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired compound was prepared using the method described in Example 403H starting with N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, prepared as in Example 403G, and N-(2-Cyclohexylethyl)-N-(furan-2-ylmethyl)amine, prepared as in Example 1200A. m/e (ESI) 577 (MH⁺)

14810

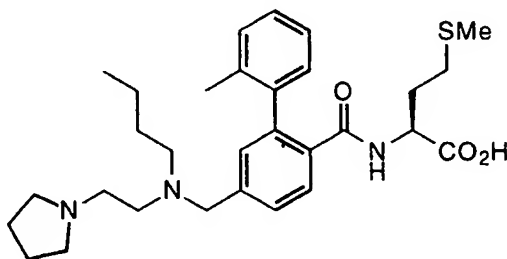
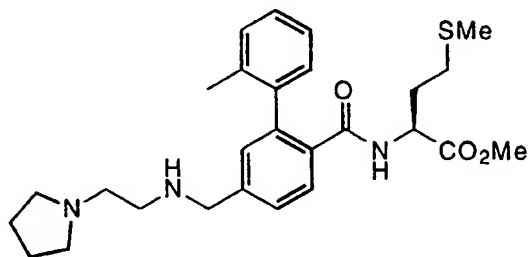


14815

Example 1200CN-[4-N-(2-Cyclohexylethyl)-N-(furan-2-ylmethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I starting with the compound in Example 1200B. ^1H (300MHz, CDCl_3 , δ) 7.81 (1H, d, J=8Hz), 7.56 (1H, m), 7.42 (1H, d, J=2Hz), 7.30-7.10 (5H, m), 6.37 (2H, bs), 6.15 (1H, d, J=8Hz), 4.45 (1H, m), 4.10-3.80 (4H, m), 2.67 (2H, m), 2.20-2.05 (5H, m), 2.00 (3H, s), 1.90 (1H, m), 1.80-1.40 (8H, m), 1.30-1.00 (4H, m), 0.88 (2H, m). m/e (ESI) 561 (MH^+) Anal. calc. for $\text{C}_{33}\text{H}_{42}\text{N}_2\text{O}_4\text{S} \cdot 1.00 \text{ H}_2\text{O}$ C 68.25, H 7.64, N 4.82 Found C 67.94, H 7.34, N 4.65

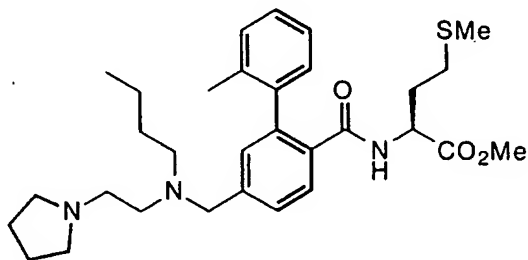
14825

Example 1201

14830

Example 1201AN-[4-N-(2-Pyrrolidin-1-ylethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

14835 The desired compound was prepared using the method described in Example 403H starting with N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, prepared as in Example 403G, and 1-(2-aminoethyl)pyrrolidine. m/e (ESI) 484 (MH⁺)

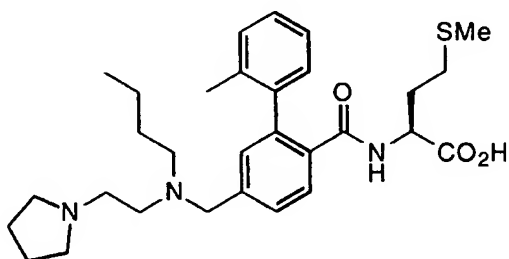


Example 1201B

14840 N-[4-N-Butyl-N-(2-pyrrolidin-1-ylethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired compound was prepared using the method described in Example 403H starting with the compound prepared in Example 1201A and butyraldehyde. m/e (ESI) 540 (MH⁺)

14845

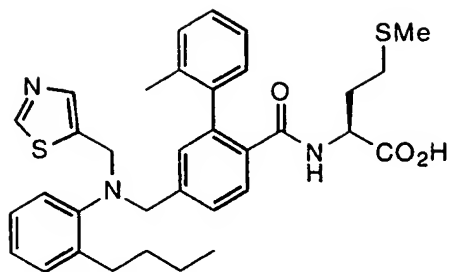


Example 1201C

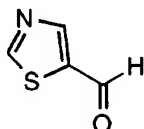
N-[4-N-Butyl-N-(2-pyrrolidin-1-ylethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine

14850 The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1201B. ¹H (300MHz, CDCl₃, δ) 7.66 (1H, d, J=8Hz), 7.35-7.10 (5H, m), 7.09 (1H, bs), 6.37 (1H, m), 4.36 (1H, m), 3.63 (2H, s), 3.16 (4H, m), 3.03 (2H, m), 2.84 (2H, m), 2.43 (2H, bt, J=8Hz), 2.20-1.80 (13H, m), 1.65 (1H, m), 1.41 (2H, m), 1.23 (2H, m), 0.85 (3H, t, J=8Hz). m/e (ESI) 524 (MH⁺)

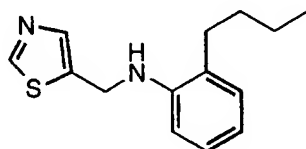
14855 Anal.calc. for C₃₀H₄₃N₃O₃S·1.00 H₂O C 66.27, H 8.34, N 7.73 Found C 65.92, H 8.29, N 7.59



14860

Example 1202Example 1202A5-Thiazolecarboxaldehyde

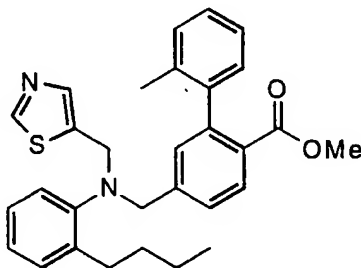
14865 The desired compound was prepared according to the method of Example 403G starting with 5-hydroxymethylthiazole. ^1H (300MHz, CDCl_3 , δ) 10.13 (1H, s), 9.12 (1H, s), 8.54 (1H, s).



14870

Example 1202BN-(2-Butylphenyl)-N-(thiazol-5-ylmethyl)amine

The desired compound was prepared according to the method of Example 403H starting with 2-butylaniline and the aldehyde from Example 1202A. m/e (DCI) 247 (MH^+)

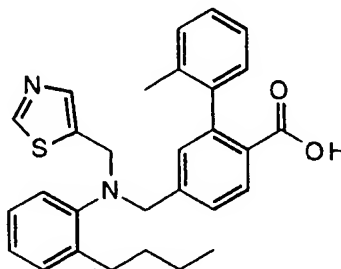


14875

Example 1202C

4-N-(2-Butylphenyl)-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoic acid
methyl ester

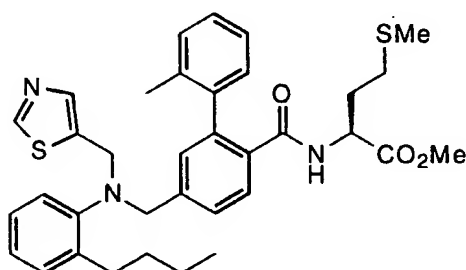
The desired compound was prepared according to the method of Example 1174B
 14880 starting with 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as in
 Example 1178A-D, and the compound from Example 1202B.



Example 1202D

14885 4-N-(2-Butylphenyl)-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoic acid

The desired acid was prepared using the method described in Example 403E starting
 with the product from Example 1202C.

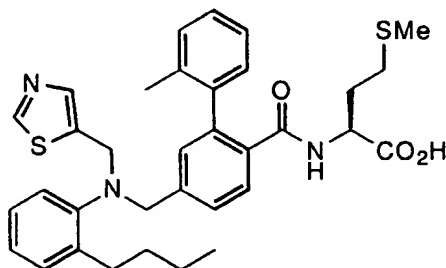


Example 1202E

N-[4-N-(2-Butylphenyl)-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine methyl ester

The desired compound was prepared using the method described in Example 403F
 starting with the product from Example 1202D. m/e (ESI) 614 (MH⁺)

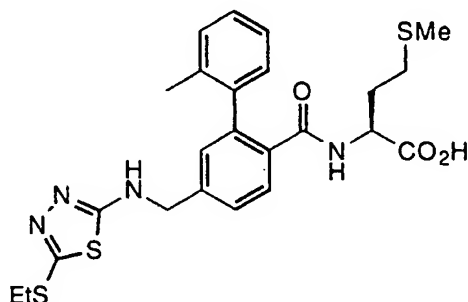
14895



Example 1202F

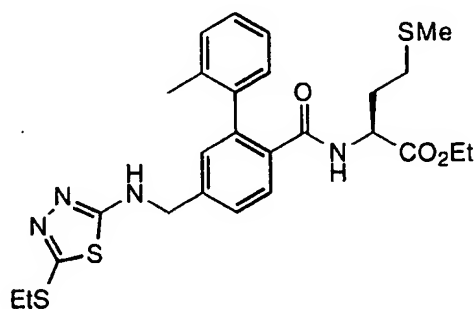
N-[4-N-(2-Butylphenyl)-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine

14900 The desired compound was prepared according to the method of Example 403I
 starting with the compound from Example 1202E. ^1H (300MHz, CDCl_3 , δ) 8.73 (1H, s),
 7.91 (1H, bt, $J=8\text{Hz}$), 7.66 (1H, bs), 7.40-7.15 (5H, m), 7.15-6.90 (5H, bs), 5.88 (1H,
 d, $J=8\text{Hz}$), 4.57 (1H, m), 4.29 (2H, s), 4.13 (2H, s), 2.72 (2H, bt, $J=8\text{Hz}$), 2.20-1.80
 (9H, m), 1.55 (3H, m), 1.35 (2H, m), 0.88 (3H, t, $J=8\text{Hz}$). m/e (ESI) 600 (MH^+)
 14905 Anal. calc. for $\text{C}_{34}\text{H}_{39}\text{N}_3\text{O}_3\text{S}_2$ C 67.86, H 6.53, N 6.98 Found C 67.57, H 6.43, N 6.71



Example 1203

14910



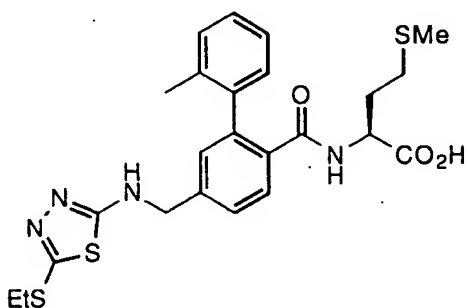
Example 1203A

N-[4-N-((2-Ethylthio)-1,3,4-thiadiazol-5-yl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine ethyl ester

14915 2-Amino-5-(ethylthio)-1,3,4-thiadiazole (419 mg, 2.60 mmol) and N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester (1.00 g, 2.60 mmol), prepared as in Example 403G, were mixed with toluene (4 mL) and refluxed under N_2 with a Dean-Stark trap overnight. Reaction diluted with EtOAc and washed with water and brine. Organic layer dried with Na_2SO_4 , filtered, and concentrated in vacuo. To a solution of this
 14920 residue in EtOH (8 mL) at 0°C under N_2 was added sodium borohydride (98 mg, 2.60 mmol), and mixture stirred vigorously at ambient temperature for 3 hours. Reaction diluted with EtOAc and washed with water and brine. Organic layer dried with Na_2SO_4 , filtered, and concentrated in vacuo. Residue purified by flash chromatography on silica gel eluting

with 60% EtOAc/Hexanes to afford the desired product as a pale yellow oil (347 mg, 25%).

14925 m/e (ESI) 543 (MH⁻)



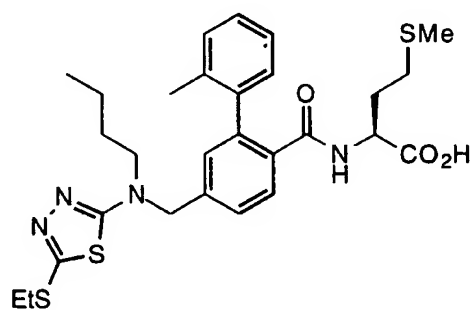
Example 1203B

N-[4-N-((2-Ethylthio)-1,3,4-thiadiazol-5-yl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine

14930

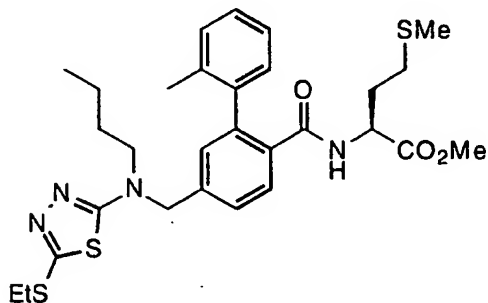
The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1203A. ¹H (300MHz, CDCl₃, δ) 7.88 (1H, m), 7.46 (1H, m), 7.30-7.00 (5H, m), 5.94 (2H, m), 4.58 (1H, m), 4.42 (2H, bd, J=8Hz), 3.13 (2H, q, J=8Hz), 2.20-1.80 (9H, m), 1.67 (1H, m), 1.39 (3H, t, J=8Hz). m/e (ESI) 515 (MH⁻) Anal.calc. for C₂₄H₂₈N₄O₃S₃·0.50 H₂O C 54.83, H 5.56, N 10.66 Found C 54.86, H 5.41, N 11.04

14935



14940

Example 1204

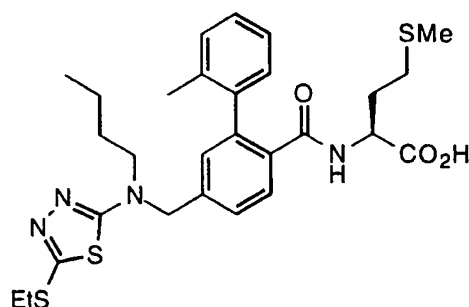


Example 1204A

N-[4-N-Butyl-N-((2-ethylthio)-1,3,4-thiadiazol-5-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

14945

The desired compound was prepared using the method described in Example 403H starting with the compound prepared as in Example 1203A (methyl ester) and butyraldehyde. m/e (ESI) 587 (MH⁺)



14950

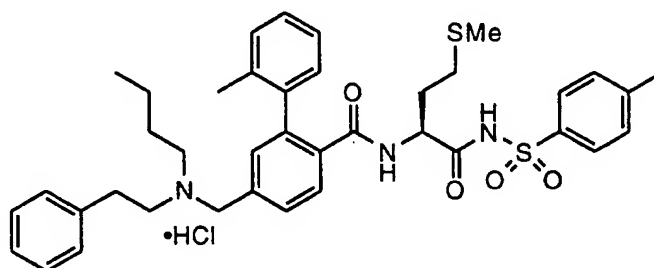
Example 1204B

N-[4-N-Butyl-N-((2-ethylthio)-1,3,4-thiadiazol-5-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

14955

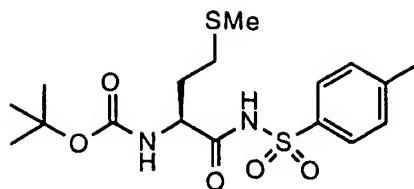
The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1204A. ¹H (300MHz, CDCl₃, δ) 7.81 (1H, m), 7.43 (1H, bd, J=8Hz), 7.30-7.10 (5H, m), 6.00 (1H, d, J=8Hz), 5.38 (2H, m), 4.48 (1H, m), 3.17 (2H, m), 3.02 (2H, q, J=8Hz), 2.20-1.80 (9H, m), 1.60 (3H, m), 1.32 (5H, t, J=8Hz), 0.88 (3H, t, J=8Hz). m/e (ESI) 571 (MH⁻) Anal.calc. for C₂₈H₃₆N₄O₃S₃·0.50 H₂O C 57.80, H 6.41, N 9.63 Found C 57.79, H 6.11, N 9.52

14960

Example 1216

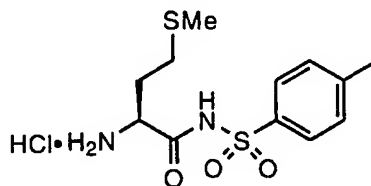
N-[4-(N-Butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine p-tolylsulfonimide hydrochloride salt

14965

Example 1216AN-(tert-Butoxycarbonyl)-methionine p-tolylsulfonimide

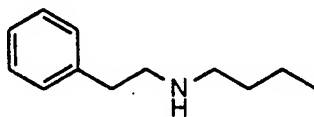
14970 N-(tert-Butoxycarbonyl)-methionine (960 mg, 3.85 mmol) was dissolved in CH_2Cl_2 (50 mL), then added EDCI•HCl (1.12 g, 5.85 mmol), DMAP (287 mg, 2.35 mmol), and p-toluenesulfonamide (1.71 g, 10.0 mmol). The reaction was stirred at RT overnight, concentrated, dissolved in EtOAc (130 mL), then washed with water, 2N HCl, water, and brine. After drying over Na_2SO_4 , filtration, and concentration, the compound

14975 was purified by chromatography using 1/1 hex/ EtOAc, then EtOAc. Recovered 635 mg (41%). MS (APCI) 403 (M+H)⁺.

Example 1216BMethionine p-tolylsulfonimide hydrochloride salt

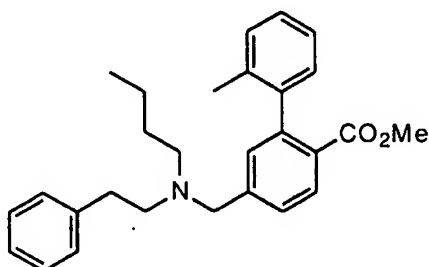
14980 The compound described in Example 1216A (610 mg, 1.52 mmol) was dissolved in 4N HCl in dioxane (10 mL), stirred at RT for 45 min., then diluted with Et_2O . The resultant solids were filtered off, and washed with Et_2O to give 465 mg (90%) white solids. MS (DCI/ NH_3) 303 (M+H)⁺.

14985

Example 1216CN-Butyl-2-phenylethylamine

14990 2-Phenethylamine (12.5 mL, 12.1 g, 99.5 mmol), butyraldehyde (13.2 mL, 10.8 g, 150 mmol), and 3Å molecular sieves were stirred at 50 °C for 1 h, then at RT for 5.5 h. The reaction was then diluted with CH_2Cl_2 , filtered through celite, then concentrated to an oil. That oil was dissolved in absolute EtOH (150 mL-previously cooled to 0 °C), and NaBH_4 (5.7 g, 150 mmol) was added. The reaction was stirred at RT overnight, concentrated, partitioned between water and Et_2O , then the organic layer was washed with

14995 water and brine. After drying over Na_2SO_4 , filtration, and concentration, the compound was purified by vacuum distillation using a 6" Vigreux column (98-100 °C/ 9 mm). Recovered 8.2 g (46%). ^1H NMR (CDCl_3) δ 7.30 (m, 2H), 7.20 (m, 3H), 2.84 (m, 4H), 2.61 (dd, 2H), 1.43 (m, 2H), 1.32 (m, 2H), 1.08 (br s, 1H), 0.88 (t, 3H).

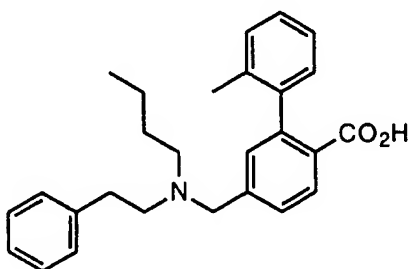


15000

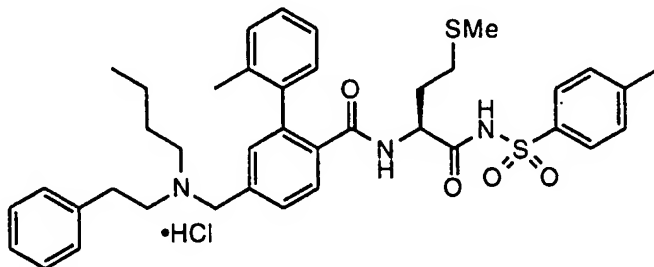
Example 1216D4-(N-Butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester

The title compound was prepared from the compound described in Example 1216C and the bromide described in Example 1178D using the method of Example 1178G. MS

15005 (APCI) 416 ($\text{M}+\text{H}$) $^+$.

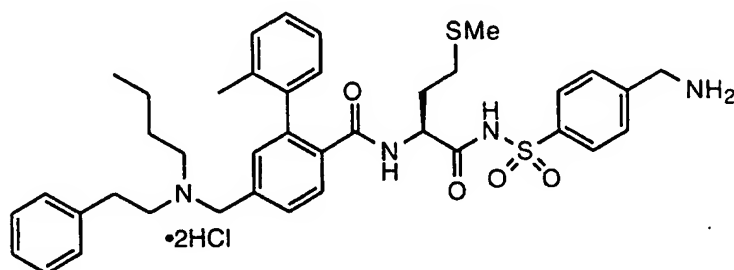
Example 1216E4-(N-Butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoic acid

15010 The title compound was prepared from the compound described in Example 1216D using the method of Example 1178H. MS (ESI) 402 ($\text{M}+\text{H}$) $^+$.

Example 1216F

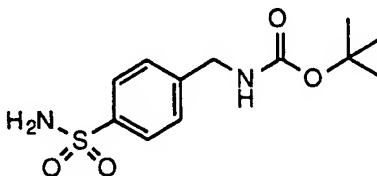
15015 N-[4-(N-Butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine p-tolylsulfonimide hydrochloride salt

The above compound was prepared according to the method of Example 1205D using the compounds described in Examples 1216B and 1216E, except the order of the aqueous work-up was saturated NaHCO₃, 2N HCl, brine, and the chromatography used 98/2/0.5 CHCl₃/MeOH/CH₃CO₂H. ¹H NMR (CDCl₃) δ 7.85 (m, 4H), 7.26 (m, 12H), 6.47 (m, 1H), 4.60 (m, 1H), 4.30 (m, 2H), 3.20 (m, 6H), 2.43 (s, 3H), 2.08 (m, 3H), 1.90 (m, 7H), 1.83, 1.60 (both m, total 4H), 0.95 (m, 3H). MS (ESI) 684 (M-H)⁻. Anal calcd for C₃₉H₄₈ClN₃O₄S₂: C, 64.84; H, 6.70; N, 5.82; Cl, 4.91. Found: C, 64.62; H, 6.82; N, 5.69; Cl, 4.62.



Example 1217

15030 N-[4-(N-Butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine 4-(aminomethyl)phenylsulfonimide dihydrochloride salt

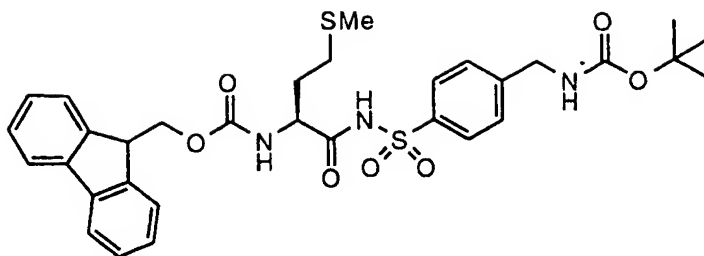


Example 1217A

4-[(tert-Butoxycarbonyl)aminomethyl]phenylsulfonamide

15035 4-(Aminomethyl)phenylsulfonamide hydrochloride salt hemihydrate (1.0 g, 4.3 mmol) was dissolved in CH₂Cl₂ (20 mL), then triethylamine (0.66 mL, 0.48 g, 4.8 mmol) and di-tert-butyl-dicarbonate (0.95 g, 4.3 mmol) were added. The reaction was stirred at RT overnight, then concentrated and partitioned between water and EtOAc. The organic layer was washed with 2N HCl, saturated aqueous NaHCO₃ and brine, then dried over Na₂SO₄.

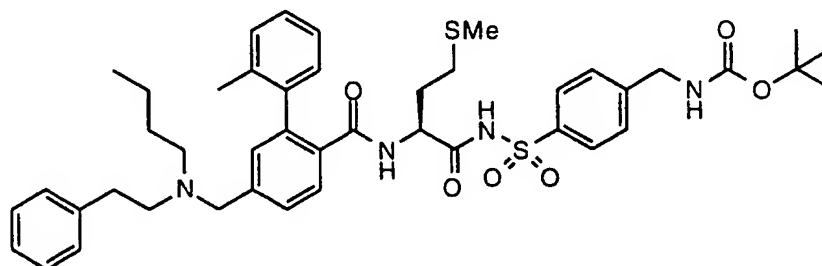
15040 After filtration and concentration recovered 1.3 g tacky white solids. MS (DCI/NH₃) 304 (M+H+NH₃)⁺.

Example 1217B

15045 N-(9-Fluorenylmethoxycarbonyl)-methionine 4-[(tert-butoxycarbonyl)aminomethyl]phenylsulfonimide

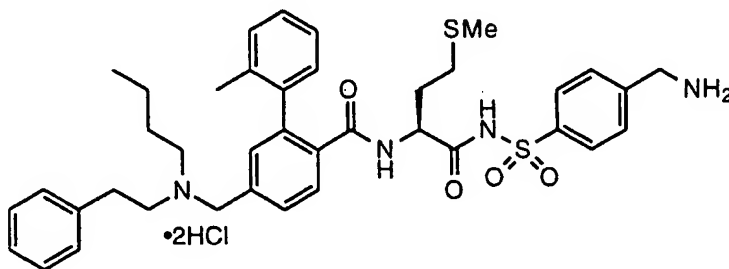
Using N-(9-Fluorenylmethoxycarbonyl)-methionine and the compound described in Example 1217A, the title compound was prepared by the method of Example 1216A. MS (ESI) 638 (M-H)⁻.

15050

Example 1217C

N-[4-(N-Butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine 4-[(tert-butoxycarbonyl)aminomethyl]phenylsulfonimide

15055 The compound described in Example 1217B was treated with piperidine in CH₂Cl₂ to give the free amine which was not purified, but directly reacted with the compound described in Example 1216E by the method of Example 1216F to give the title compound. MS (ESI) 801 (M+H)⁺.

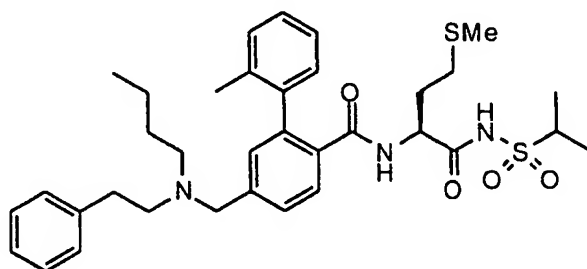


15060

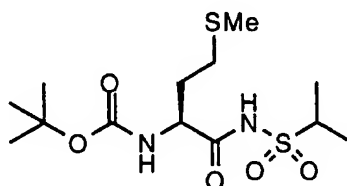
Example 1217D

N-[4-(N-Butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine 4-(aminomethyl)phenylsulfonimide dihydrochloride salt

Starting with the compound described in Example 1217C, the title compound was prepared by the method of Example 1216B. ¹H NMR (CD₃OD) δ 8.05 (d, 2H), 7.66 (m, 4H), 7.45 (br s, 1H), 7.25 (m, 10H), 4.53 (d, 2H), 4.25 (m, 1H), 4.24 (s, 2H), 3.33 (m, 2H), 3.24 (m, 2H), 3.10 (m, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80 (m, 3H), 1.60 (m, 1H), 1.40 (m, 2H), 0.98 (t, 3H). MS (ESI) 699 (M-H)⁻. Anal calcd for C₃₉H₅₀Cl₂N₄O₄S₂ · 1.50 H₂O : C, 68.49; H, 6.67; N, 7.00. Found: C, 58.41; H, 6.61; N, 6.70.

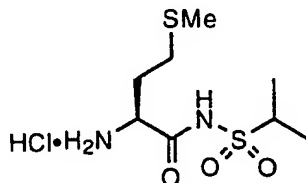
Example 1218

N-[4-(N-Butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine isopropylsulfonimide

Example 1218A

N-(tert-Butoxycarbonyl)-methionine isopropylsulfonimide

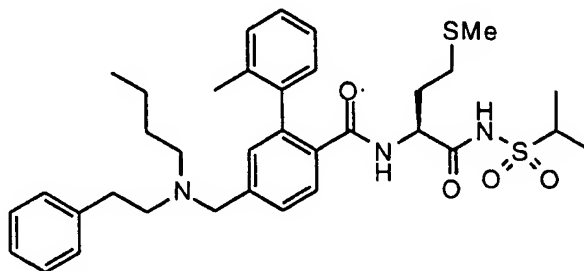
The title compound was prepared by the method of Example 1216A using isopropylsulfonamide. MS (DCI/NH₃) 372 (M+H+NH₃)⁺.

Example 1218B

Methionine isopropylsulfonimide hydrochloride salt

Starting with the compound described in Example 1218A, the title compound was prepared by the method of Example 1216B, except the product was isolated as a tan foam after stripping off the dioxane. MS (DCI/NH₃) 255 (M+H)⁺.

15090



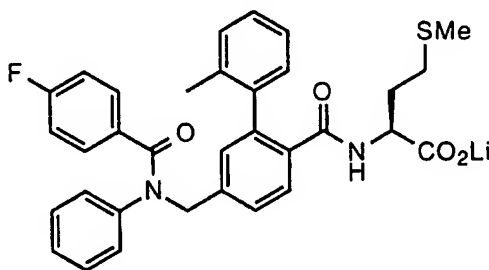
Example 1218C

N-[4-(N-Butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine isopropylsulfonimide

15095

The above compound was prepared according to the method of Example 1205D using the compounds described in Examples 1218B and 1216E, except the order of the aqueous work-up was saturated NaHCO₃, 2N HCl, brine, and the chromatography used 98/2/0.5 CHCl₃/MeOH/CH₃CO₂H. ¹H NMR (CDCl₃) δ 7.91 (m, 1H), 7.43 (d, 1H), 7.32 (m, 3H), 7.18 (m, 7H), 5.83 (d, 1H), 4.43 (m, 1H), 3.77 (s, 2H), 3.65 (m, 1H), 2.80 (br s, 4H), 2.59 (m, 2H), 2.15, 2.02 (both m, total 8H), 1.82 (m, 1H), 1.50, 1.38, 1.28 (all m, total 11H), 0.86 (t, 3H). MS (ESI) 636 (M-H)⁻. Anal calcd for C₃₅H₄₇N₃O₄S₂: C, 65.90; H, 7.43 N, 6.59. Found: C, 66.01; H, 7.36; N, 6.30.

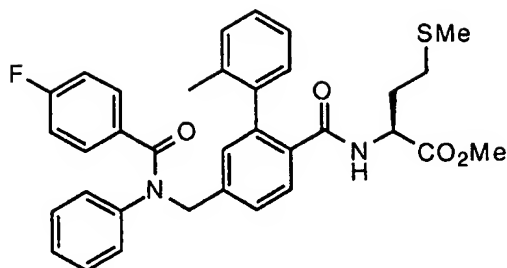
15100



15105

Example 1227

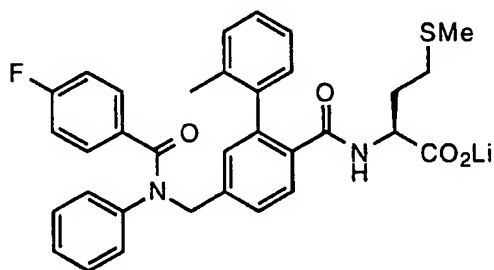
N-[4-N-(N-phenyl-N-(4-fluorobenzoyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.



15110

Example 1227AN-[4-N-(N-phenyl-N-(4-fluorobenzoyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

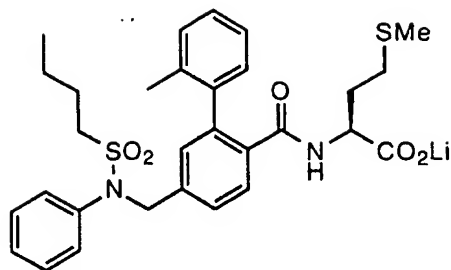
A mixture of 4-fluorobenzoyl chloride (0.053 g, 0.33 mmol), 1236C (0.103 g, 0.22
 15115 mmol), and 0.2 ml of pyridine in 5 ml of CH_2Cl_2 was stirred for 12 hours. The mixture was
 washed with 10% HCl and brine respectively, dried over MgSO_4 . Flash chromatography of
 the residue eluting with 1:1 EtOAc/Hexane afforded 0.13 g of the title compound (99%).
 NMR(CDCl_3) 7.84-7.94 (m, 1H); 7.38-7.48 (m, 1H); 7.05-7.38 (m, 10H); 5.85-5.92 (m,
 1H); 5.10-5.27 (m, 2H); 4.56-4.67 (m, 1H); 3.62 (s, 3H); 1.95-2.20 (m, 8H); 1.7-2.0 (m,
 15120 1H); 1.5-1.7 (m, 1H). (ESI/ NH_3)/MS: 585($\text{M}+\text{H}$)⁺; 604 ($\text{M}+\text{NH}_4$)⁺.

Example 1227BN-[4-N-(N-phenyl-N-(4-fluorobenzoyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

15125

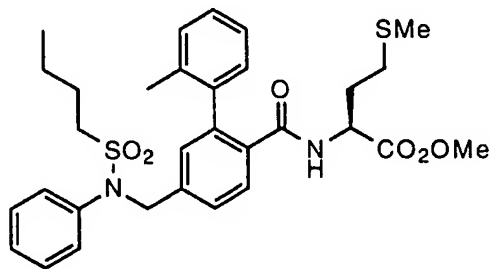
Prepared according to the procedure of example 1178J from 1227A. NMR
 ^1H ($\text{MeOH}-d_4$): 7.6-7.7 (1H, m); 7.3-7.5 (3H, m); 6.9-7.3 (14H, m); 5.18-5.38(2H, m);
 4.1-4.22 (1H, m); 1.7-2.1.(10H, m). ESI(-)/MS: 569($\text{M}-\text{Li}$).

15130

Example 1228

N-[4-N-(N-phenyl-N-(n-butanesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

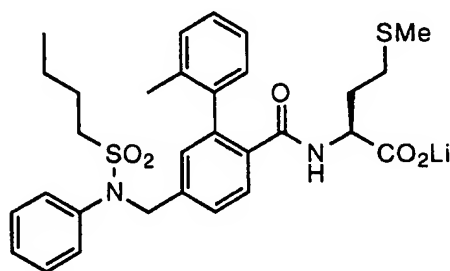
15135

Example 1228A

N-[4-N-(N-phenyl-N-(n-butanesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

15140

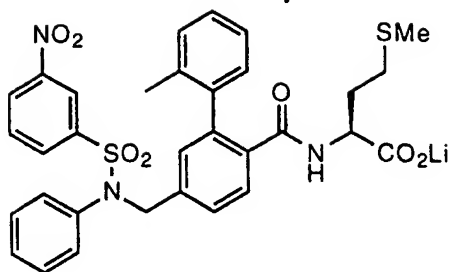
Prepared to the procedure of example 1229A from the reaction between 1236C and butanesulfonyl chloride. NMR(CDCl₃) 7.80-7.90 (m, 1H); 7.12-7.38 (m, 10H); 7.05-7.11 (m, 1H); 5.8-5.9 (m, 1H); 4.78 (s, 2H); 4.5-4.65 (m, 1H); 3.62 (s, 3H); 3.0-3.08 (m, 2H); 1.5-2.15 (m, 14H); 0.92-0.98 (m, 3H). (DSI/NH₃)/MS: 583(M+H)⁺; 600(M+NH₄)⁺.

Example 1228B

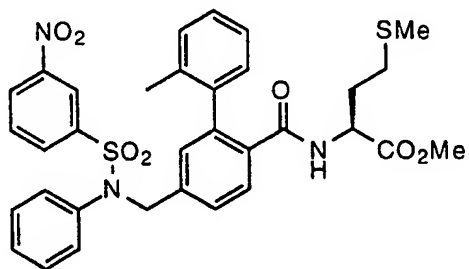
N-[4-N-(N-phenyl-N-(n-butanesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

15145

Prepared according to the procedure of example 1178J from 1228A. NMR
 15150 ¹H(MeOH-d₄): 7.5-7.62 (1H, m); 7.1-7.4 (12H, m); 4.95 (2H, s); 4.1-4.22 (1H, m); 3.1-3.2 (2H, t); 1.7-2.1 (12H, m); 1.4-1.5 (2H, m); 0.9-1.0 (3H, t). ESI(-)/MS: 567(M-Li).

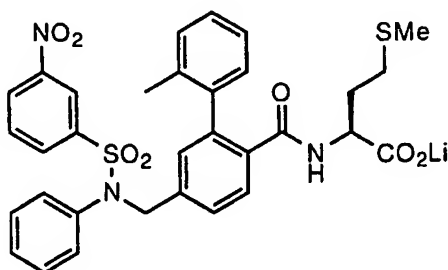
Example 1229

N-[4-N-(N-phenyl)-N-(3-nitrobenzenesulfonyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

Example 1229A

N-[4-N-(N-phenyl)-N-(3-nitrobenzenesulfonyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

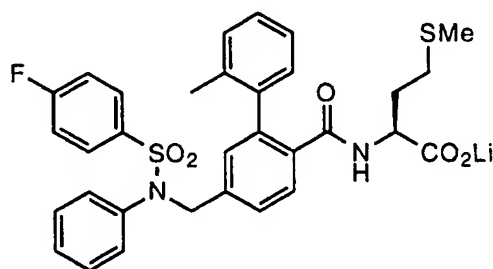
A mixture of 3-nitrophenylsulfonyl chloride (0.076 g, 0.34 mmol), 1236C (0.106 g, 0.23 mmol), and 0.2 ml of pyridine in 3 ml of CH_2Cl_2 was stirred for 12 hours. The mixture was washed with 10% HCl and brine respectively, dried over MgSO_4 . Flash chromatography of the residue eluting with 1:1 EtOAc/Hexane afforded 0.12 g of the title compound (80%). NMR(CDCl_3) 8.56 (m, 1H); 8.40-8.48 (m, 1H); 7.9-7.95 (m, 1H); 7.8-7.91 (m, 1H); 7.68-7.76 (m, 1H); 7.10-7.35 (m, 8H); 7.05 (m, 1H); 6.95-7.01 (m, 2H); 5.8-5.9 (m, 1H); 4.81 (s, 2H); 4.5-4.65 (m, 1H); 3.68 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (ESI/ NH_3)/MS: 648($\text{M}+\text{H}$)⁺; 665($\text{M}+\text{NH}_4$)⁺.



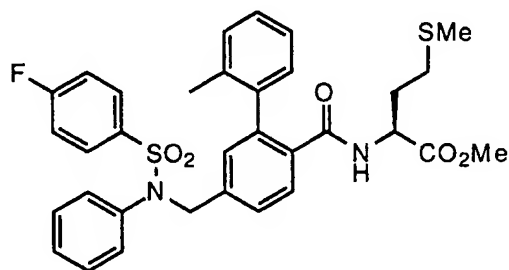
Example 1229B

N-[4-N-(N-phenyl-N-(3-nitrobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Prepared according to the procedure of example 1178J from 1229A. NMR ^1H (MeOH- d_4): 8.35-8.45 (2H, m); 7.78-7.85 (2H, m), 7.5-7.6 (1H, m); 7.3-7.4 (1H, m); 7.1-7.3 (8H, m); 6.95-7.15 (3H, m); 4.9 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 632(M-Li).

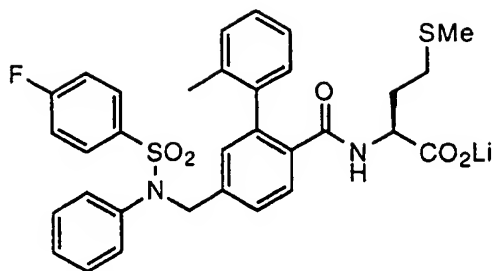
Example 1230

N-[4-N-(N-phenyl-N-(4-fluorobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Example 1230A

N-[4-N-(N-phenyl-N-(4-fluorobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1229A from reaction between 1236C and 4-fluorophenylsulfonyl chloride. NMR(CDCl_3) 7.78-7.82 (m, 1H); 7.58-7.68 (m, 2H); 7.25-7.32 (m, 10H); 7.08 (m, 1H); 6.95-7.01 (m, 2H); 5.8-5.9 (m, 1H); 4.79 (s, 2H); 4.5-4.65 (m, 1H); 3.62 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (ESI/ NH_3)/MS: 621(M+ NH_4) $^+$; 638(M+ NH_4) $^+$.

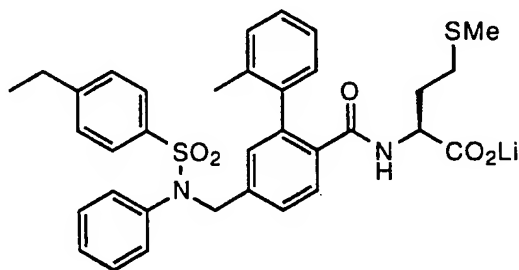
Example 1230B

N-[4-N-(N-phenyl-N-(4-fluorobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

15200

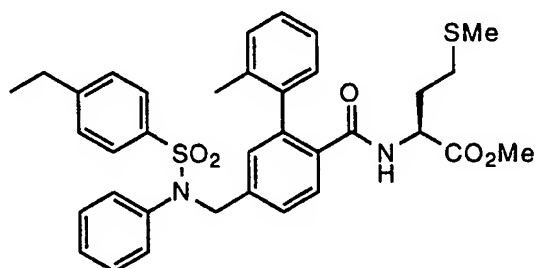
Prepared according to the procedure of example 1178J from 1230A. NMR ^1H (MeOH- d_4): 7.65-7.8 (2H, m); 7.5-7.6 (1H, m); 7.1-7.3 (1H, m); 6.95-7.1 (3H, m); 4.9 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 605(M-Li).

15205

Example 1231

N-[4-N-(N-phenyl-N-(4-ethylbenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

15210

Example 1231A

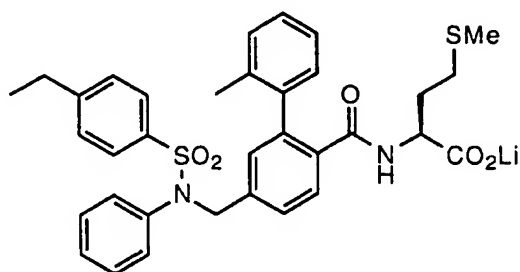
N-[4-N-(N-phenyl-N-(4-ethylbenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

15215

Prepared according to the procedure of example 1229A from reaction between 1236C and 4-ethylphenylsulfonyl chloride. NMR(CDCl_3) 7.78-7.82 (m, 1H); 7.55-7.60 (m, 2H); 7.25-7.32 (m, 10H); 7.08 (m, 1H); 6.95-7.01 (m, 2H); 5.8-5.9 (m, 1H); 4.76 (s,

2H); 4.5-4.65 (m, 1H); 3.62 (s, 3H); 2.7-2.78(m, 2H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H); 1.2-1.35(m, 3H). (DSI/NH₃)/MS: 631(M+H)⁺; 648(M+NH₄)⁺.

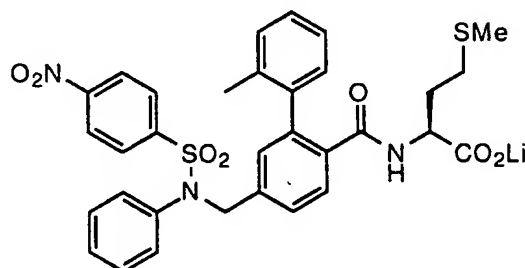
15220

Example 1231

N-[4-N-(N-phenyl-N-(4-ethylbenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

15225

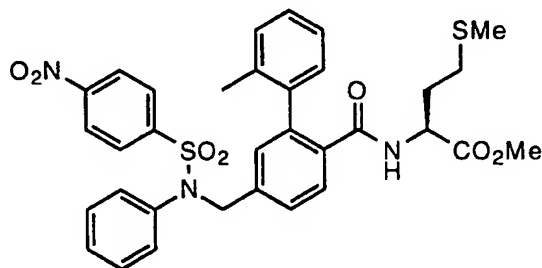
Prepared according to the procedure of example 1178J from 1231A. NMR ¹H(MeOH-d₄): 7.5-7.6 (3H, m); 7.1-7.4 (9H, m); 6.95-7.1 (3H, m); 4.9 (2H, s); 4.1-4.22 (1H, m); 2.7 (2H, q) 1.7-2.1 (10H, m) (1H, m); 1.25 (3H, t). ESI(-)/MS: 615(M-Li).



15230

Example 1232

N-[4-N-(N-phenyl-N-(4-nitrobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

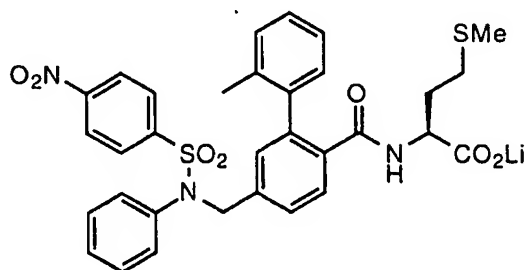


15235

Example 1232A

N-[4-N-(N-phenyl-N-(4-nitrobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

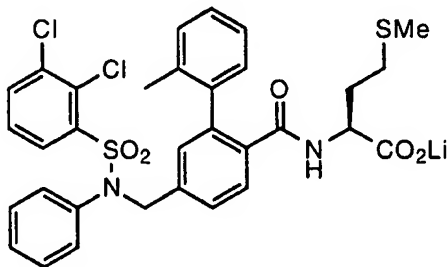
Prepared according to the procedure of example 1229A from reaction between 1236C and 4-nitrophenylsulfonyl chloride. NMR(CDC_l₃) 8.56 (m, 1H); 8.40-8.48 (m, 1H); 7.9-7.95 (m, 1H); 7.8-7.91 (m, 1H); 7.68-7.76 (m, 1H); 7.10-7.35 (m, 8H); 7.05 (m, 1H); 6.95-7.01 (m, 2H); 5.8-5.9 (m, 1H); 4.81 (s, 2H); 4.5-4.65 (m, 1H); 3.68 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 648(M+H)⁺; 665(M+NH₄)⁺.



Example 1232B

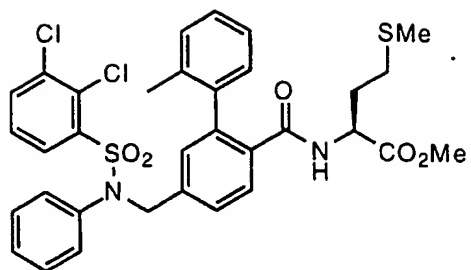
N-[4-N-(N-phenyl-N-(4-nitrobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Prepared according to the procedure of example 1178J from 1232A. NMR ¹H(MeOH-d₄): 8.45-8.55 (1H, m); 8.35-8.38 (1H, m); 8.0-8.1 (1H, m); 7.8-7.9 (1H, m); 7.5-7.7 (1H, m); 7.3-7.4 (1H, m); 7.1-7.3 (8H, m); 6.95-7.1 (3H, m); 4.9 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 632(M-Li).



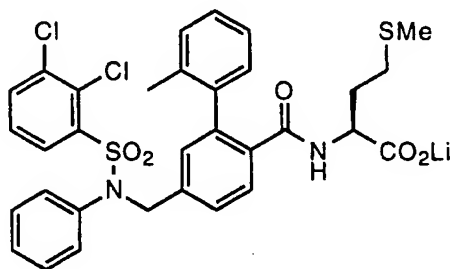
Example 1233

N-[4-N-(N-phenyl-N-(2,3-dichlorobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

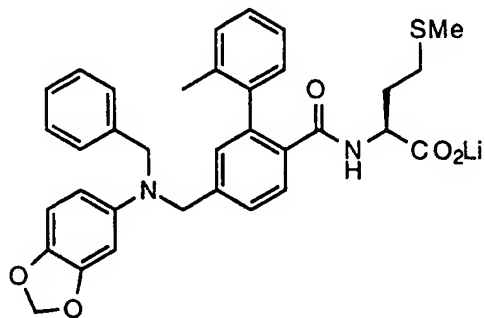
Example 1233AN-[4-N-(N-phenyl-N-(2,3-dichlorobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

15265 Prepared according to the procedure of example 1229A from reaction between 1236C and 3,4-dichlorophenylsulfonyl chloride. NMR(CDCl₃) 7.6-7.7 (m, 1H); 7.5-7.55 (m, 1H); 7.55-7.6 (m, 1H); 7.40-7.43 (m, 1H); 7.15-7.36 (m, 8H); 7.08 (m, 1H); 6.95-7.01 (m, 2H); 5.8-5.9 (m, 1H); 4.78 (s, 2H); 4.5-4.65 (m, 1H); 3.62 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 671(M+NH₄)⁺.

15270

Example 1233BN-[4-N-(N-phenyl-N-(2,3-dichlorobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

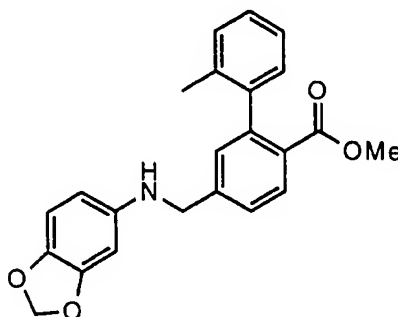
15275 Prepared according to the procedure of example 1178J from 1233A. NMR ¹H(MeOH-d₄): 7.7-7.8 (2H, m); 7.5-7.6 (2H, m); 7.1-7.3 (9H, m); 6.95-7.1 (3H, m); 4.9 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 655(M-Li).



15280

Example 1234

N-[4-N-(N-3,4-(methylenedioxy)phenyl)-N-(4-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

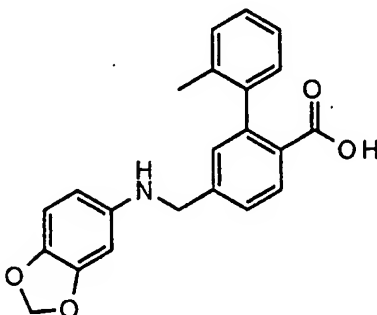


15285

Example 1234A

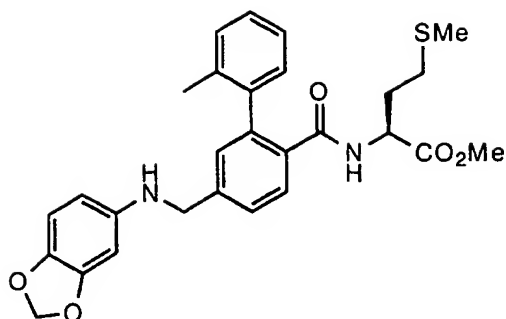
Prepared according to the procedure of example 1236A. Instead of using aniline, 3,4-(methylenedioxy)aniline was used to make the title compound. NMR(CDCl₃) 7.90-7.96 (m, 1H); 7.38-7.42 (m, 1H); 7.18-7.30 (m, 4H); 7.00-7.18 (m, 1H); 6.80-6.83 (m, 1H); 6.22-6.26 (m, 1H); 6.00-6.08 (m, 1H); 5.82 (s, m); 4.32-4.39 (m, 2H); 3.95-4.00 (m, 1H); 3.60 (s, 3H); 2.05 (s, 3H). (ESI/NH₃)/MS: 376(M+H)⁺; 373(M+NH₄)⁺.

15290

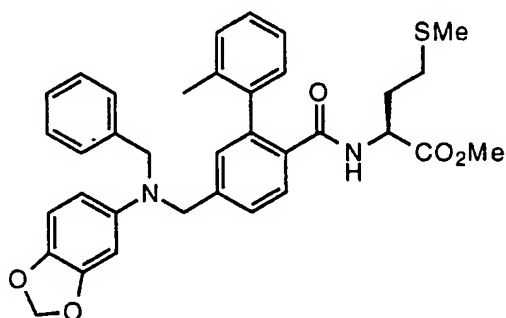
Example 1234B

Prepared according to the procedure of example 1178H from 1234A. NMR(CDCl₃) 7.90-7.96 (m, 1H); 7.38-7.42 (m, 1H); 7.18-7.30 (m, 4H); 7.00-7.18 (m, 1H); 6.80-6.83 (m, 1H); 6.22-6.26 (m, 1H); 6.00-6.08 (m, 1H); 5.82 (s, 2H); 4.32-4.39 (m, 2H); 3.95-4.00 (m, 1H); 2.05 (s, 3H). (ESI/NH₃)/MS: 362(M+H)⁺; 351(M+NH₄)⁺.

15295

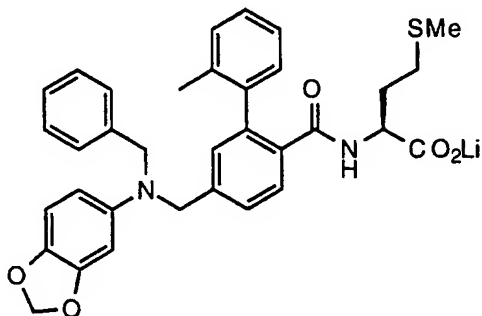
**Example 1234C**

Prepared according to the procedure of example 1178I from 1234B. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.18-7.30 (m, 6H); 7.00-7.18 (m, 1H); 6.6-6.65 (m, 1H); 6.35-6.40 (m, 1H); 6.10-6.20 (m, 1H); 5.82 (m, 3H); 4.5-4.70 (m, 3H); 3.61 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 507(M+H)⁺; 324(M+NH₄)⁺.

**Example 1234D**

N-[4-N-(N-(3,4-methylenedioxy)phenyl-N-(4-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1236A from reaction between 1235C and benzyl bromide. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.18-7.30 (m, 10H); 7.02-7.18 (m, 1H); 6.6-6.65 (m, 1H); 6.35-6.40 (m, 1H); 6.15-6.20 (m, 1H); 5.82 (m, 3H); 4.59-4.70 (m, 3H); 4.57 (s, 2H); 3.62 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 597(M+H)⁺.



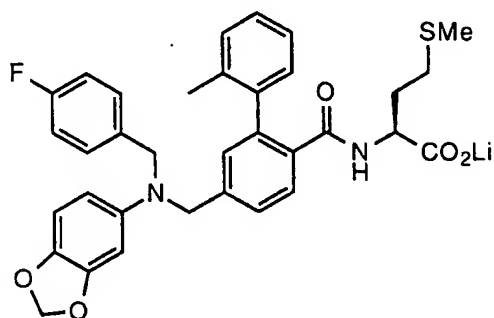
Example 1234E

N-[4-N-(N-3,4-(methylenedioxy)phenyl)-N-(4-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

15320

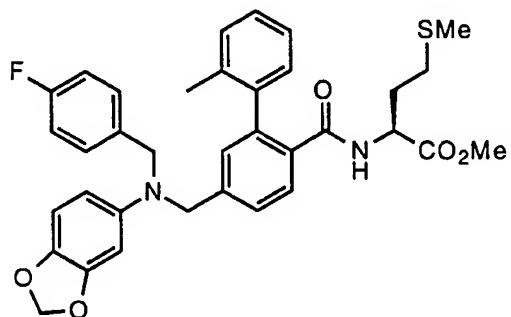
Prepared according to the procedure of example 1178J from 1234D. NMR ^1H (MeOH- d_4): 7.5-7.6 (1H, m); 7.2-7.25 (1H, m); 7.0-7.2 (9H, m); 6.9-7.0 (2H, m); 6.5-6.57 (1H, m); 6.3 (1H, m); 6.1 (1H, m); 5.75 (2H, s); 4.45 (2H, s); 4.4 (2H, s); 4.1-4.2 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 581(M-Li).

15325

Example 1235

N-[4-N-(N-3,4-(methylenedioxy)phenyl)-N-(4-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

15330

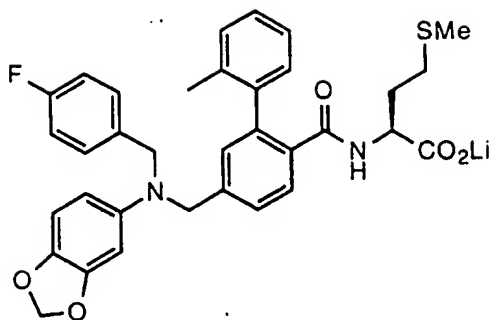
Example 1235A

N-[4-N-(N-3,4-(methylenedioxy)phenyl)-N-(4-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

15335

Prepared according to the procedure of example 1236A from reaction between 1234C and 4-fluorobenzyl bromide. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.18-7.61 (m, 7H); 6.92-7.18 (m, 3H); 6.6-6.65 (m, 1H); 6.35-6.40 (m, 1H); 6.15-6.20 (m, 1H); 5.82 (m, 3H); 4.57-4.65 (m, 1H); 4.53 (s, 2H); 4.50 (s, 2H); 3.65 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 614(M+H)⁺.

15340

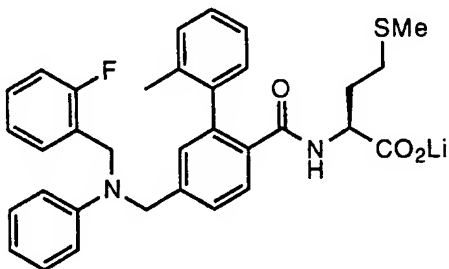
Example 1235B

N-[4-N-(N-3,4-(methylenedioxy)phenyl)-N-(4-fluorobenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

15345

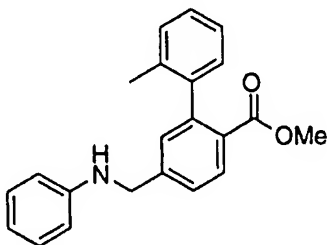
Prepared according to the procedure of example 1178J from 1235A. NMR $^1\text{H}(\text{MeOH-}d_4)$: 7.5-7.6 (1H, m); 7.2-7.25 (1H, m); 7.0-7.2 (8H, m); 6.9-7.0 (2H, m); 6.5-6.57 (1H, m); 6.3 (1H, m); 6.1 (1H, m); 5.75 (2H, s); 4.45 (2H, s); 4.4 (2H, s); 4.1-4.2 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 599(M-Li).

15350

Example 1236

N-[4-N-(N-phenyl)-N-(2-fluorobenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

15355

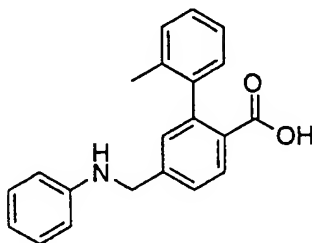
Example 1236A

4-(N-phenyl)aminomethyl-2-(2-methylphenyl)benzoic acid, methyl ester

15360

A mixture of 4-Bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (6.12 g, 20 mmol), aniline (1.68 g, 20 mmol), NaHCO_3 (1.68 g, 40 mmol), and $\text{Bu}_4\text{N}^+\text{T}^-$ (0.74 g, 2

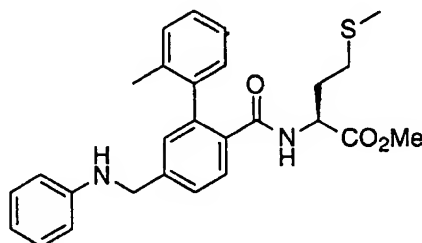
mmol) in 50 ml of DMF was heated at 75°C under N₂ for 12 hours. The reaction mixture was quenched by adding 400 ml of water. The solution was then extracted by 300 ml of EtOAc, washed by brine and dried over MgSO₄. Flash chromatography of residue on silica gel eluting with 80:20 EtOAc/Hexane afforded 6.1 g of pure product(96%). NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.40-7.45 (m, 1H); 7.0-7.36 (m, 7H); 6.68-6.78 (m, 1H); 6.58-6.65 (m, 2H); 4.2 (s, 2H); 4.05-4.2 (m, 1H); 3.58 (s, 3H); 2.05 (s, 3H). (DSI/NH₃)/MS: 332(M+H)⁺, 349(M+NH₄)⁺.



Example 1236B

4-(N-phenylaminomethyl)-2-(2-methylphenyl)benzoic acid

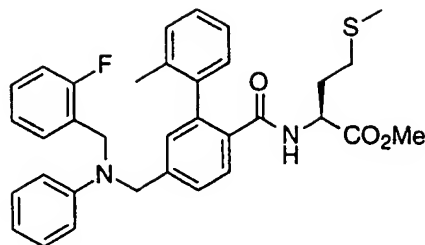
Prepared according to the procedure of example 1178H from 1236A. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.40-7.45 (m, 1H); 7.0-7.36 (m, 7H); 6.68-6.78 (m, 1H); 6.58-6.65 (m, 2H); 4.2 (s, 2H); 4.05-4.2 (m, 1H); 2.05 (s, 3H). (DSI/NH₃)/MS: 318(M+H)⁺, 335(M+NH₄)⁺.



Example 1236C

N-4-[(N-phenylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

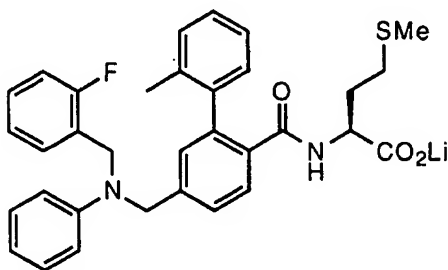
Prepared according to the procedure of example 1178I from 1236B. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.41-7.47 (m, 1H); 7.1-7.36 (m, 7H); 6.68-6.78 (m, 1H); 6.58-6.65 (m, 2H); 5.85-5.95 (m, 1H); 4.56-4.68 (m, 1H); 4.2 (s, 2H); 4.05-4.2 (m, 1H); 3.62 (s, 3H); 2.05 (s, 3H); 2.0-2.15 (m, 8H), 1.7-2.0 (m, 1H), 1.5-1.7 (m, 1H).. (DSI/NH₃)/MS: 463(M+H)⁺, 480(M+NH₄)⁺.

Example 1236DN-[4-N-(N-phenyl-N-(2-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

15390

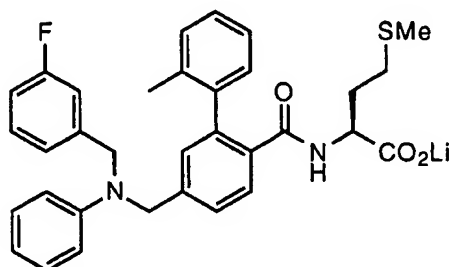
Prepared according to the procedure of 1236A from reaction between 1236C and 2-fluorobenzyl bromide. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.0-7.4 (m, 12H); 6.65-6.78 (m, 3H); 5.8-5.9 (m, 1H); 4.75 (m, 4H); 4.58-4.65 (m, 1H); 3.65 (s, 3H), 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). MS/(DSI/NH₃): 571(M+H)⁺.

15395

Example 1236EN-[4-N-(N-phenyl-N-(2-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

15400

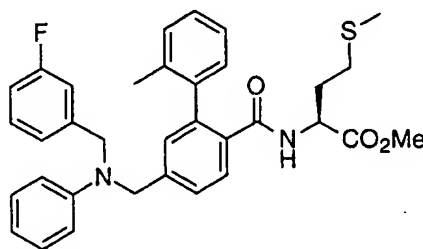
Prepared according to the procedure of example 1178J for making lithium salt. NMR ¹H(MeOH-d₄): 7.6-7.7 (1H, d); 7.3-7.4 (1H, d); 7.0-7.4 (9H, m); 6.6-6.85 (6H, m); 4.7 (2H, s); 4.65 (2H, s); 4.2-4.3 (1H, m); 1.5-2.2 (10H, m). ESI(-)/MS: 555(M-Li).



15405

Example 1237

N-[4-N-(N-phenyl-N-(3-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt



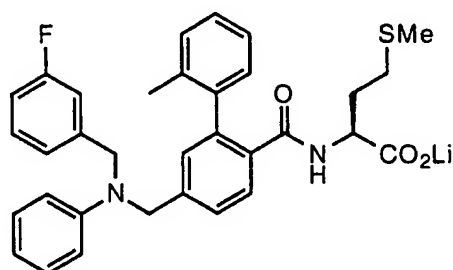
15410

Example 1237A

N-[4-N-(N-phenyl-N-(3-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of 1236A from reaction between 1236C and 3-fluorobenzyl bromide. NMR(CDCl₃) 7.85-7.95 (m, 1H); 6.9-7.4 (m, 12H); 6.75-6.8 (m, 3H); 5.8-5.9 (m, 1H); 4.70 (s, 2H); 4.58-4.65 (m, 3H); 3.62 (s, 3H); 2.0-2.15 (m, 8H), 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 571(M+H)⁺.

15415



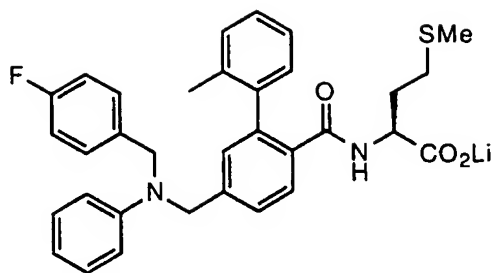
15420

Example 1237B

N-[4-N-(N-phenyl-N-(3-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

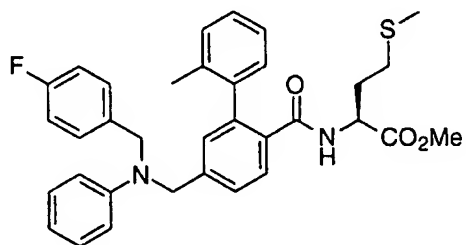
Prepared according to the procedure of example 1178J from 1237A. NMR ¹H(MeOH-d₄): 7.6-7.7 (2H, m); 6.86-7.4 (10H, m); 6.6-6.85 (4H, m); 4.75-4.85 (4H, m); 4.18-4.3 (1H, m); 1.6-2.2 (10H, m). ESI(-)/MS: 555(M-Li).

15425

Example 1238

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N-[4-N-(N-phenyl-N-(4-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Example 1238A

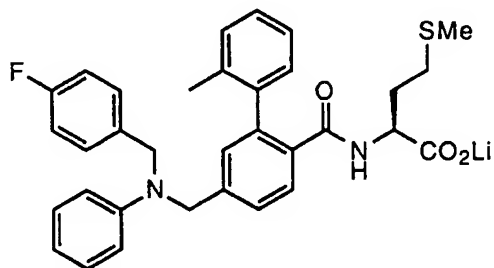
15435

N-[4-N-(N-phenyl-N-(4-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of 1236A from reaction between 1236C and 4-fluorobenzyl bromide. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.15-7.4 (m, 9H); 6.95-7.15 (m, 3H); 6.7-6.8 (m, 3H); 5.8-5.9 (m, 1H); 4.70 (s, 2H); 4.58-4.65 (m, 3H); 3.62 (s, 3H);

15440

2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 571(M+H)⁺.

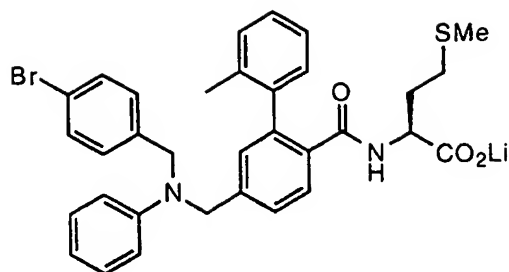
Example 1238B

15445

N-[4-N-(N-phenyl-N-(4-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

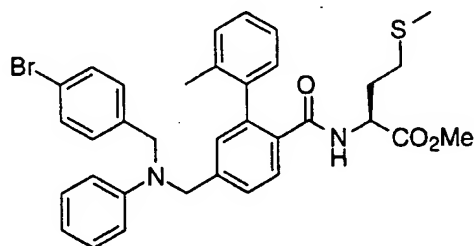
Prepared according to the procedure of example 1178J from 1238A. NMR ¹H(MeOH-d₄): 7.6-7.7 (2H, m); 6.86-7.4 (10H, m); 6.6-6.85 (4H, m); 4.65-4.85 (4H, m); 4.18-4.3 (1H, m); 1.6-2.2 (10H, m). ESI(-)/MS: 555(M-Li).

15450

Example 1239

N-[4-N-(N-phenyl-N-(4-bromobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

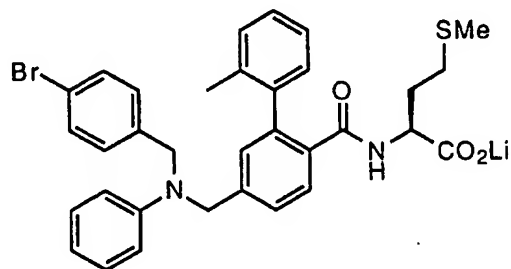
15455

Example 1239A

N-[4-N-(N-phenyl-N-(4-bromobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

15460

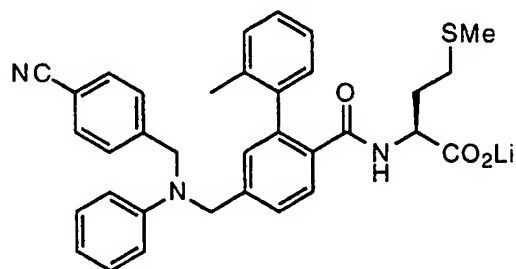
Prepared according to the procedure of example 1236A from reaction between 1236C and 4-bromobenzyl bromide. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.05-7.48 (m, 12H); 6.65-6.78 (m, 3H); 5.8-5.9 (m, 1H); 4.75 (s, 2H); 4.55-4.65 (m, 3H); 3.65 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (ESI/NH₃)/MS: 631(M+H)⁺.

Example 1239B

N-[4-N-(N-phenyl-N-(4-bromobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

15465

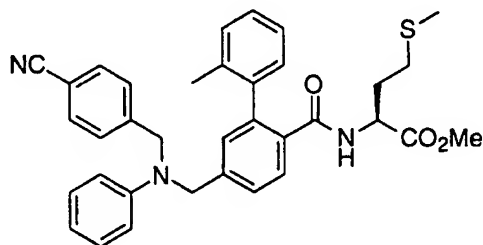
Prepared according to the procedure of example 1178J from 1239A. NMR
 15470 ^1H (MeOH- d_4): 7.58-7.67 (1H, d); 7.38-7.46 (2H, d); 7.3-7.39 (H, d); 7.0-7.3 (11H, m);
 6.6-6.8 (3H, m); 4.75 (2H, s); 4.65 (2H, s); 4.18-4.3 (1H, m); 1.5-2.2 (10H, m). ESI(-)
)/MS: 615(M-Li), 573.



15475

Example 1240

N-[4-N-(N-phenyl-N-(4-cyanobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine lithium salt

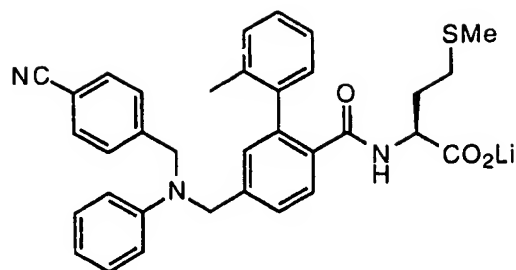


15480

Example 1240A

N-[4-N-(N-phenyl-N-(4-cyanobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1236A from reaction between
 15485 1236C and 4-cyanobenzyl bromide. NMR(CDCl_3) 7.85-7.95 (m, 1H); 7.58-7.65 (m, 2H);
 7.1-7.4 (m, 10H); 6.65-6.80 (m, 3H); 5.8-5.9 (m, 1H); 4.65 (m, 4H); 4.58-4.64 (m, 1H);
 3.65 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/ NH_3)/MS:
 578(M+H) $^+$.

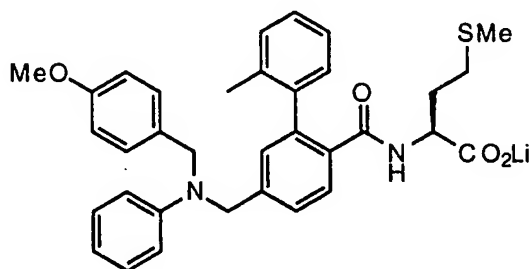


15490

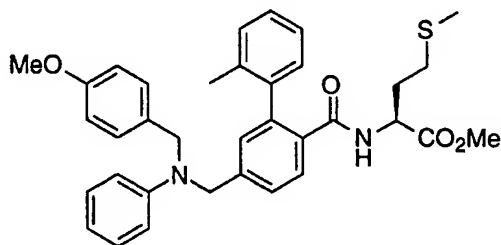
Example 1240BN-[4-N-(N-phenyl-N-(4-cyanobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Prepared according to the procedure of example 1178J from 1240A. NMR

15495 ^1H (MeOH- d_4): 7.6-7.7 (3H, m); 7.4-7.5 (2H, m); 7.35-7.4 (1H, m); 7.02-7.3 (10H, m); 6.6-6.7 (3H, m) 4.9 (2H, s); 4.75 (2H, s); 4.18-4.3 (1H, m); 1.5-2.2 (10H, m). ESI(-)/MS: 562(M-Li).



15500

Example 1241N-[4-N-(N-phenyl-N-(4-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

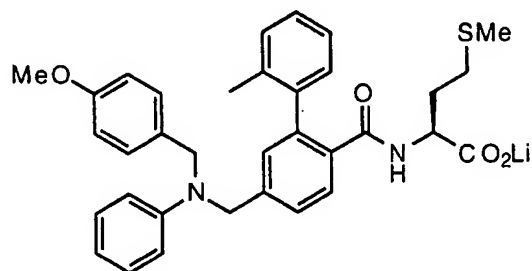
15505

Example 1241AN-[4-N-(N-phenyl-N-(4-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1236A from reaction between

15510 1236C and 4-methoxybenzyl bromide. NMR(CDCl_3) 7.85-7.95 (m, 1H); 7.15-7.4 (m,

12H); 6.8-6.9 (m, 1H); 6.7-6.8 (m, 2H); 5.8-5.9 (m, 1H); 4.65 (m, 3H); 4.60 (s, 2H); 3.81 (s, m); 3.65 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 583(M+H)⁺.



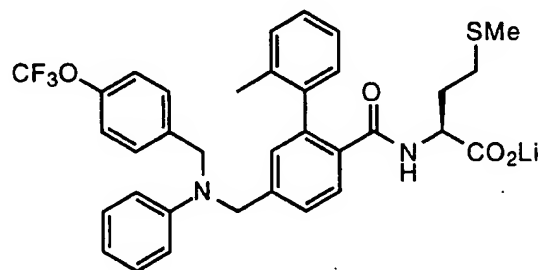
15515

Example 1241B

N-[4-N-(N-phenyl-N-(4-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Prepared according to the procedure of example 1178J from 1241A. NMR

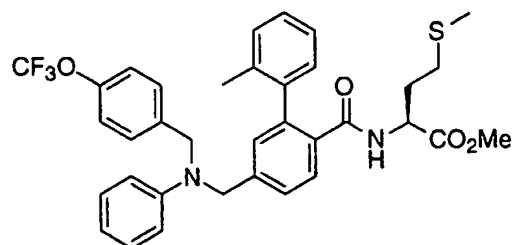
15520 ¹H(MeOH-d₄): 7.6-7.7 (1H, m); 7.0-7.3 (10H, m); 6.6-6.85 (6H, m); 4.68 (2H, s); 4.58 (2H, s); 4.18-4.3 (1H, m); 3.88 (3H, s); 1.5-2.2 (10H, m). ESI(-)/MS: 567(M-Li); 445.



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Example 1242

N-[4-N-(N-phenyl-N-(4-trifluoromethoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

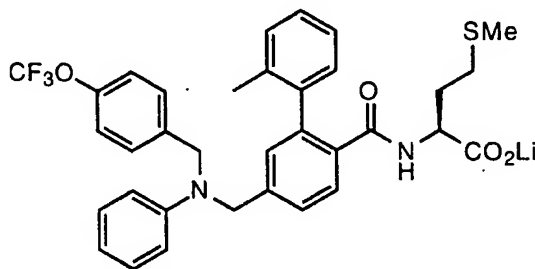


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Example 1242A

N-[4-N-(N-phenyl-N-(4-trifluoromethoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1236A from reaction between 1236C and 4-trifluoromethoxybenzyl bromide. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.15-7.4 (m, 12H); 6.8-6.9 (m, 1H); 6.7-6.8 (m, 2H); 5.8-5.9 (m, 1H); 4.65 (m, 3H); 4.60 (s, 2H); 3.65 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (ESI/NH₃)/MS: 636(M+H)⁺.

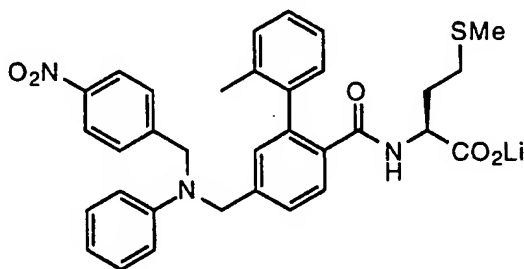


15540

Example 1242B

N-[4-N-(N-phenyl-N-(4-trifluoromethoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

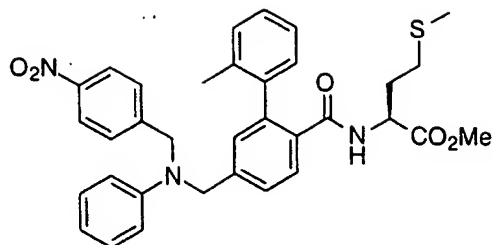
Prepared according to the procedure of example 1178J from 1242A. NMR ¹H(MeOH-d₄): 7.6-7.7 (1H, m); 7.3-7.4 (3H, d), 7.05-7.25 (9H, m); 6.7-6.8 (2H, m); 6.6-6.7 (1H, m); 4.7-4.8 (4H, m); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 621(M-Li).



15550

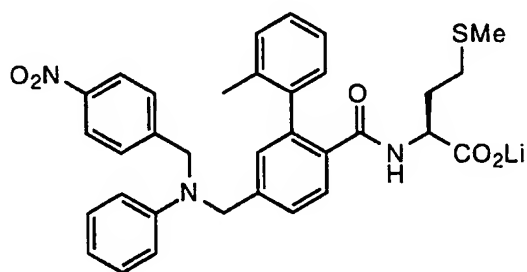
Example 1243

N-[4-N-(N-phenyl-N-(4-nitrobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Example 1243A

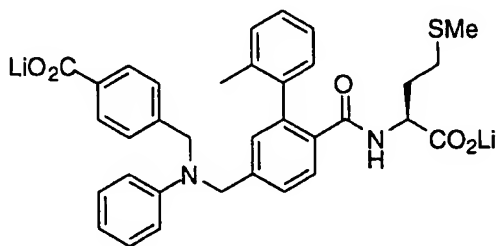
N-[4-N-(N-phenyl-N-(4-nitrobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

Prepared according to the procedure of example 1236A from reaction between 1236C and 4-nitrobenzyl bromide. NMR(CDCl₃) 8.15-8.20 (m, 2H); 7.85-7.95 (m, 1H); 7.1-7.45 (m, 10H); 6.75-6.81 (m, 1H); 6.65-6.71 (m, 2H); 5.78-5.88 (m, 1H); 4.7-4.8 (ss, 4H); 4.6-4.75 (m, 1H); 3.65 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 598(M+H)⁺; 615 (M+NH₄)⁺.

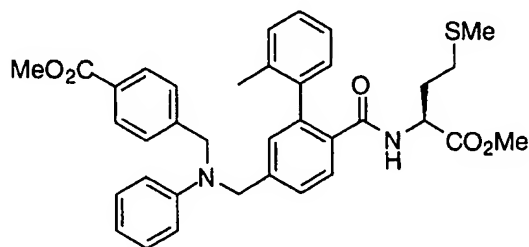
Example 1243B

N-[4-N-(N-phenyl-N-(4-nitrobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Prepared according to the procedure of example 1178J from 1243A. NMR ¹H(MeOH-d₄): 8.15-8.2 (2H, m); 7.6-7.7 (1H, m), 7.48-7.56 (2H, m); 7.35-7.41 (1H, m); 7.15-7.3 (8H, m); 6.65-6.78 (3H, m), 4.78-4.85(4H, m); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 582(M-Li).

Example 1244

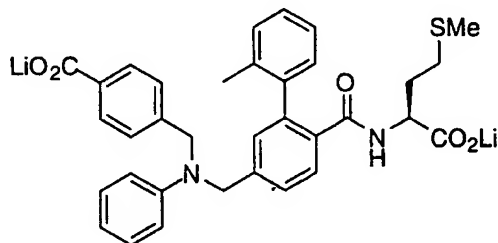
N-[4-N-(N-phenyl-N-(4-carboxylic acid benzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, dilithium salt



Example 1244A

N-[4-N-(N-phenyl-N-(4-carboxylic acid benzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, dimethyl ester

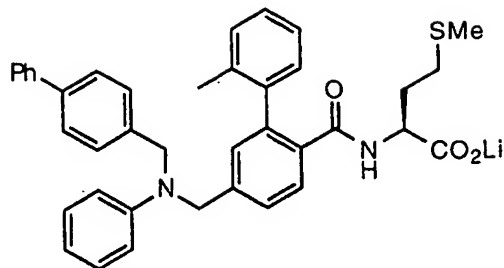
Prepared according to the procedure of example 1236A from reaction between 1236C and methyl 4-(bromomethyl) benzoate. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.18-7.40 (m, 12H); 6.7-6.85 (m, 3H); 5.8-5.9 (m, 1H); 4.7 (s, 4H); 4.58-4.68 (m, 1H); 3.90 (s, 3H); 3.68 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (ESI/NH₃)/MS: 628(M+NH₄)⁺.



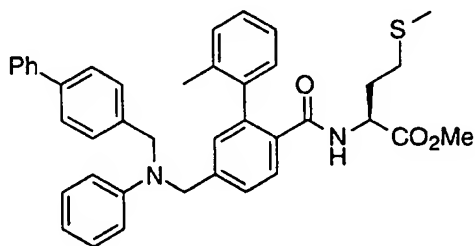
Example 1244B

N-[4-N-(N-phenyl-N-(4-carboxylic acid benzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, dilithium salt

Prepared according to the procedure of example 1178J from 1244A. NMR ¹H(MeOH-d₄): 7.9-8.0 (2H, m); 7.6-7.7 (1H, m), 7.3-7.4 (2H, m); 7.1-7.28 (9H, m); 6.7-6.75 (2H, m); 6.6-6.7 (1H, m); 4.78 (2H, s); 4.70 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 595(M-Li).

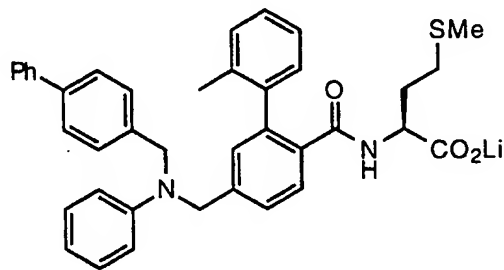
Example 1245

N-[4-N-(N-phenyl)-N-(4-phenylbenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

Example 1245 A

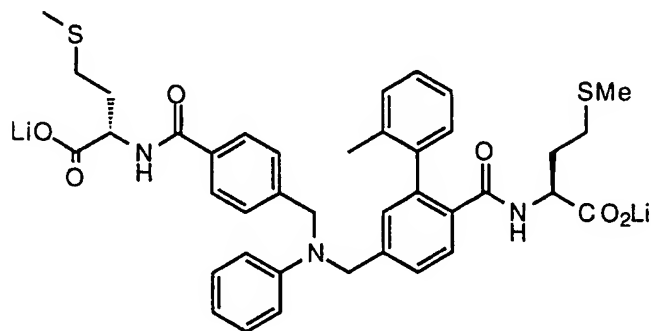
N-[4-N-(N-phenyl)-N-(4-phenylbenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1236A from reaction between 1236C and 4-phenylbenzyl bromide. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.1-7.45 (m, 17H); 6.75-6.81 (m, 1H); 6.65-6.7 (m, 3H); 5.8-5.9 (m, 1H); 4.7-4.8 (ss, 4H); 4.6-4.75 (m, 1H); 3.65 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 629(M+H)⁺.

Example 1245B

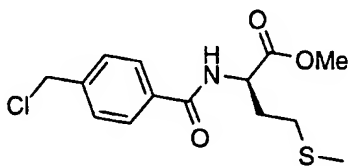
N-[4-N-(N-phenyl)-N-(4-phenylbenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

Prepared according to the procedure of example 1178J from 1245A. NMR
 ^1H (MeOH- d_4): 7.1-7.7 (19H, m); 6.7-6.8 (2H, m); 6.6-6.7 (1H, m); 4.7-4.8 (4H, m);
 15620 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 613(M-Li).



Example 1246

15625 N-[4-N-(N-phenyl-N-(4-N-carboxymethionine)benzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine dilithium salt.

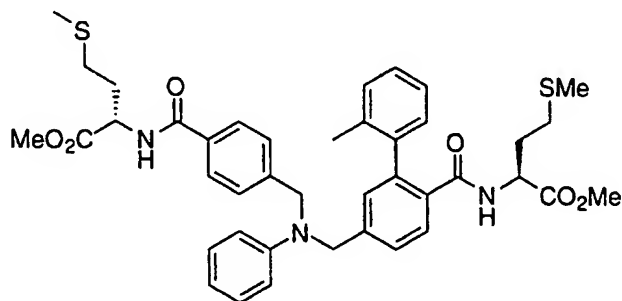


Example 1246A

15630 4-(chloromethyl)-benzoyl methionine, methyl ester

A mixture of 4-(chloromethyl)-benzoyl chloride (0.189 g, 1 mmol), methionine methyl ester hydrochloride (0.199 g, 1 mmol), and 0.5 ml of pyridine in 5 ml of chloroform was stirred for 12 hours. The organic solution was washed with 10 % HCl, brine, and dried over MgSO_4 . Flash chromatography of the residue afforded 0.20 g of desired product

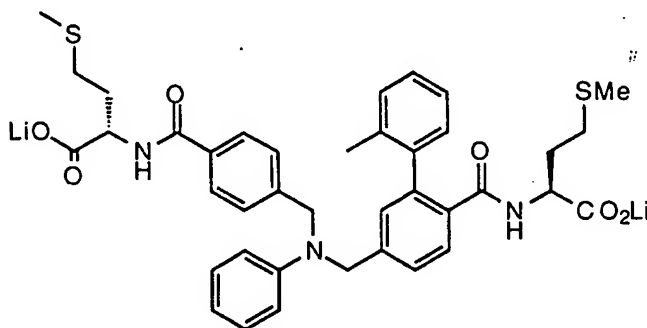
15635 (64%). NMR(CDCl_3) 7.80-7.85 (m, 2H); 7.28-7.32 (m, 2H); 6.9-7.0 (m, 1H); 4.9-5.0 (m, 1H); 4.60 (s, 2H); 3.80 (s, 3H); 3.68 (s, 3H); 2.35-2.45 (m, 2H); 2.12-2.35 (m, 1H); 2.1-2.2 (m, 1H). (ESI/ NH_3)/MS: 316(M+H) $^+$; 333(M+ NH_4) $^+$.



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Example 1246BN-[4-N-(N-phenyl-N-(4-N-carboxymethionine)benzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, dimethyl ester

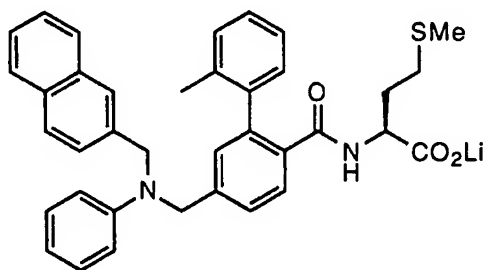
Prepared according to the procedure of example 1236A from the reaction between 1236C and 1246A. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.75-7.80 (m, 2H); 7.18-7.35 (m, 9H); 7.10 (s, 1H); 6.9-6.95 (m, 1H); 6.68-6.78 (m, 3H); 5.8-5.9 (m, 1H); 4.81 (s, 2H); 4.5-4.65 (m, 1H); 3.80 (s, 3H); 3.68 (s, 3H); 2.35-2.45 (m, 2H); 2.12-2.35 (m, 1H); 2.0-2.15 (m, 9H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 742(M+H)⁺.



15650

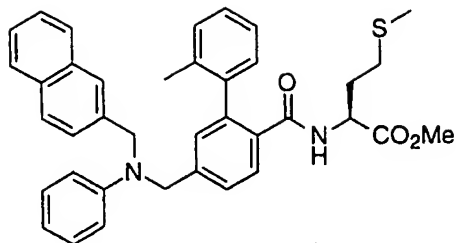
Example 1246CN-[4-N-(N-phenyl-N-(4-N-carboxymethionine)benzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine dilithium salt.

Prepared according to the procedure of example 1178J from 1246B. NMR ¹H (d₄-MeOH): 7.8-7.9 (2H, m); 7.6-7.7 (1H, m); 7.3-7.4 (4H, m); 7.2 (4H, m); 7.1 (4H, m); 6.7-6.75 (2H, m); 6.6-6.7 (1H, m); 4.8 (4H, m); 4.5-4.6 (1H, m); 4.2-4.3 (1H, m); 2.5-2.65 (2H, m); 1.6-2.3 (15H, m). ESI(-)/MS: 711 (M-Li); 733 (M+Na-2H).



15660

Example 1247N-[4-N-(N-phenyl-N-(2-naphthyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt



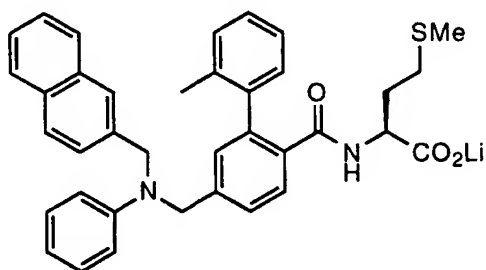
15665

Example 1247A

N-[4-N-(N-phenyl-N-(2-naphthyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

15670

Prepared according to the procedure of example 1236A from reaction between 1236C and 2-bromomethyl-naphthalene. NMR(CDCl₃) 7.68-7.95 (m, 5H); 7.18-7.45 (m, 11H); 7.1 (s, 1H); 6.7-6.85 (m, 3H); 5.8-5.9 (m, 1H); 4.80 (s, 2H); 4.76 (s, 2H); 4.56-4.7 (m, 1H); 3.68 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 603(M+H)⁺.



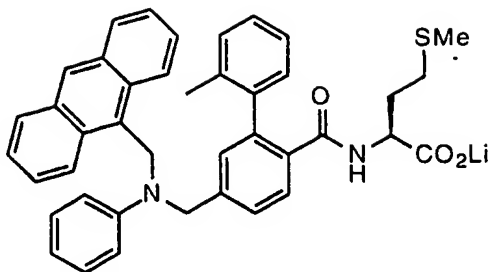
15675

Example 1247B

N-[4-N-(N-phenyl-N-(2-naphthyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

15680

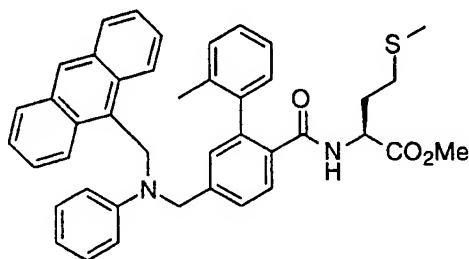
Prepared according to the procedure of example 1178J from 1247A. NMR ¹H(MeOH-d₄): 7.78-7.84 (2H, m); 7.6-7.8 (3H, m), 7.3-7.5 (4H, d); 7.0-7.25 (8H, m); 6.8-7.0 (2H, m); 6.75-6.82 (2H, m); 6.6-6.6 (1H, m); 4.8 (2H, s); 4.85 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 587(M-Li).



15685

Example 1248

N-[4-N-(N-phenyl-N-(9-methyl-anthracene-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt



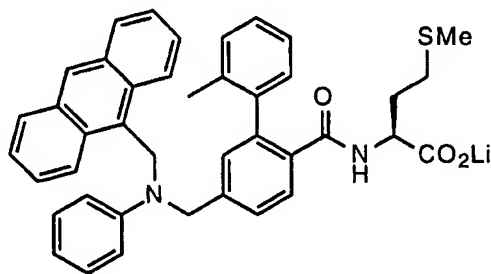
15690

Example 1248A

N-[4-N-(N-phenyl-N-(9-methyl-anthracene-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1236A from reaction between

15695 1236C and 9-bromomethyl-anthracene. NMR(CDCl₃) 8.4 (s, 1H); 8.1-8.2 (m, 2H); 7.9-8.0 (m, 2H); 7.0-7.65 (m, 12H); 7.1 (s, 1H); 6.8-6.95 (m, 3H); 5.8-5.9 (m, 1H); 5.45 (s, 2H); 4.68 (m, 1H); 4.25 (s, 2H); 3.60 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 653(M+H)⁺.



15700

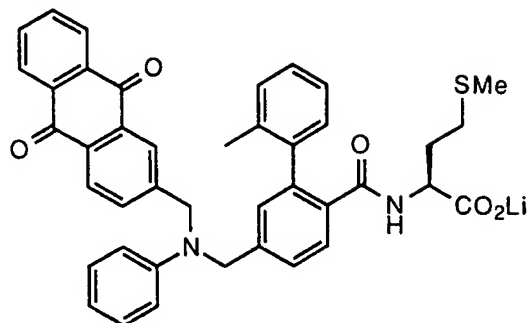
Example 1248B

N-[4-N-(N-phenyl-N-(9-methyl-anthracene-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Prepared according to the procedure of example 1178J from 1248A. NMR

15705 ¹H(MeOH-d₄): 8.45 (1H, s); 8.17-8.22 (2H, m), 7.9-8.05 (2H, m); 7.1-7.5 (13H, m),

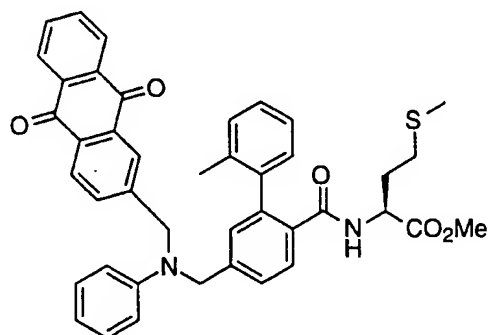
6.8-6.95 (3H, m); 6.5-6.67 (1H, m); 5.45 (2H, s); 4.5 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 637(M-Li).



15710

Example 1249

N-[4-N-(N-phenyl-N-(2-methyl-anthraquinone-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt



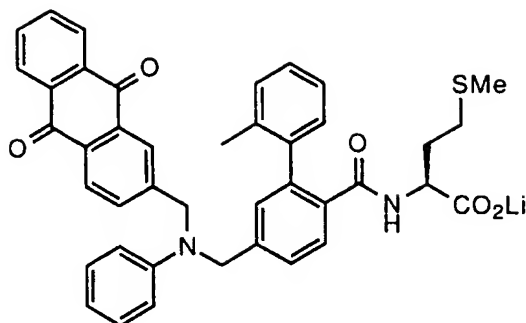
15715

Example 1249A

N-[4-N-(N-phenyl-N-(2-methyl-anthraquinone-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1236A from reaction between

15720 1236C and 2-bromomethyl-anthraquinone. NMR(CDCl₃) 8.4 (s, 1H); 8.0-8.35 (m, 3H); 7.9-8.0 (m, 2H); 7.0-7.65 (m, 11H); 6.8-6.95 (m, 3H); 5.8-5.9 (m, 1H); 4.8 (s, 2H); 4.78 (s, 2H); 4.56-4.7 (m, 1H); 3.63 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 683(M+H)⁺.

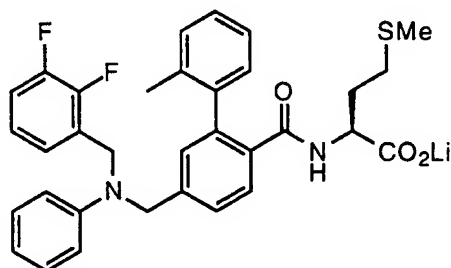


15725

Example 1249B

N-[4-N-(N-phenyl)-N-(2-methyl-anthraquinone-yl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

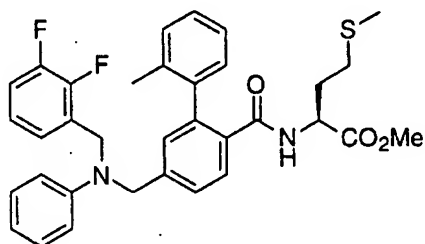
Prepared according to the procedure of example 1178J from 1249A. NMR
 15730 ^1H (MeOH- d_4): 8.1-8.3 (4H, m); 7.8-7.9 (2H, m), 7.7-7.8 (1H, m); 7.6-7.7 (1H, m);
 7.25-7.35 (1H, m); 7.0-7.3 (8H, m); 6.75-6.8 (2H, m); 6.6-6.7 (1H, m); 4.9 (2H, s); 4.8
 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 667(M-Li).



15735

Example 1250

N-[4-N-(N-phenyl)-N-(2,3-difluorobenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

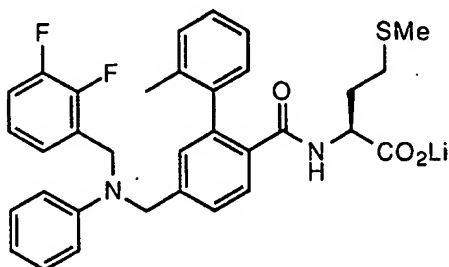


15740

Example 1250A

N-[4-N-(N-phenyl)-N-(2,3-difluorobenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1236A from reaction between
 15745 1236C and 2,3-difluorobenzyl bromide. NMR(CDCl₃) 7.85-7.95 (m, 1H); 6.95-7.40 (m, 11H); 6.68-6.8 (m, 3H); 5.8-5.9 (m, 1H); 4.75 (s, 2H); 4.70 (s, 2H); 4.60-4.70 (m, 1H); 3.70 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 589(M+H)⁺.

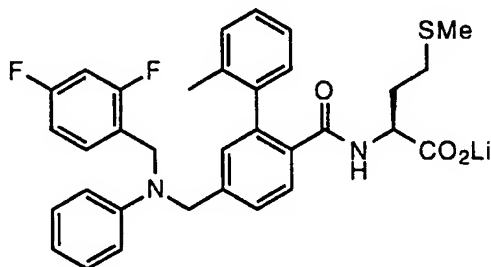


15750

Example 1250B

N-[4-N-(N-phenyl-N-(2,3-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

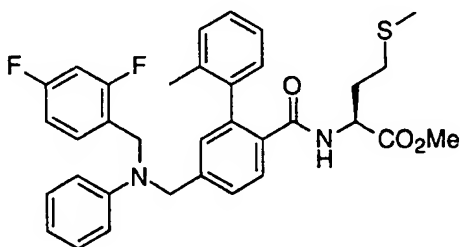
Prepared according to the procedure of example 1178J from 1250A. NMR
 15755 ¹H(MeOH-d₄): 7.7-7.8 (1H, m); 7.3-7.4 (1H, m), 7.0-7.28 (11H, m); 6.65-6.75 (3H, m); 4.8-4.85 (4H, m); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 573(M-Li).



15760

Example 1251

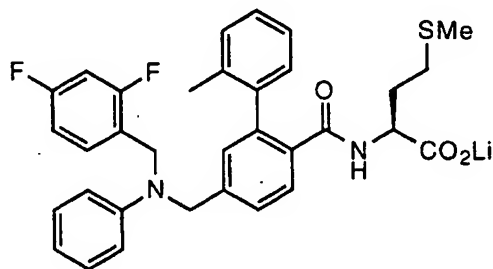
N-[4-N-(N-phenyl-N-(2,4-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt



15765

Example 1251A*N*-[4-*N*-(*N*-phenyl)-*N*-(2,4-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

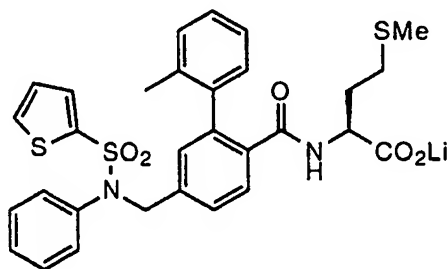
Prepared according to the procedure of example 1236A from reaction between 1236C and 2,4-difluorobenzyl bromide. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.18-7.40 (m, 9H); 7.1 (s, 1H); 6.7-6.85 (m, 4H); 5.8-5.9 (m, 1H); 4.7 (s, 2H); 4.68 (m, 3H); 3.68 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (ESI/NH₃)/MS: 589(M+H)⁺.

Example 1251B

15775

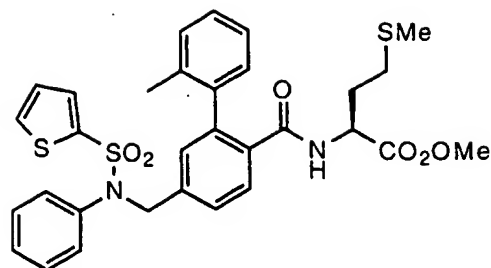
N-[4-*N*-(*N*-phenyl)-*N*-(2,4-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Prepared according to the procedure of example 1178J from 1251A. NMR ¹H(MeOH-d₄): 7.6-7.68 (1H, m); 7.3-7.4 (1H, m), 7.3-7.4 (1H, d); 7.0-7.3 (9H, m); 6.8-7.0 (2H, m); 6.6-6.8 (3H, m); 4.70 (2H, s); 4.75 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 573(M-Li).

Example 1255

15785

N-[4-*N*-(*N*-phenyl)-*N*-(2-thiophenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

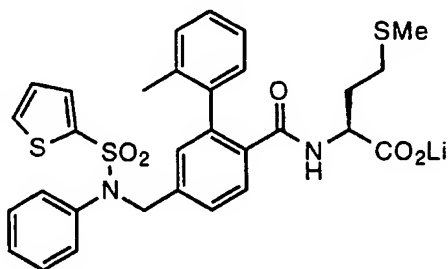
Example 1255A

15790

N-[4-*N*-(*N*-phenyl-*N*-(2-thiophenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

15795

Prepared according to the procedure of example 1229A from reaction between 1236C and 2-thiophenesulfonyl chloride. NMR(CDCl₃) 7.75-7.82 (m, 1H); 7.60-7.62 (m, 1H); 7.39-7.42 (m, 1H); 7.12-7.38 (m, 9H); 7.05-7.11 (m, 2H); 6.95-7.05 (m, 2H); 5.8-5.9 (m, 1H); 4.78 (s, 2H); 4.5-4.65 (m, 1H); 3.62 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (ESI/NH₃)/MS: 609(M+H)⁺; 626(M+NH₄)⁺.

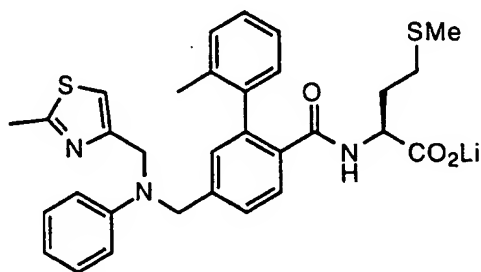
Example 1255B

15800

N-[4-*N*-(*N*-phenyl-*N*-(2-thiophenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

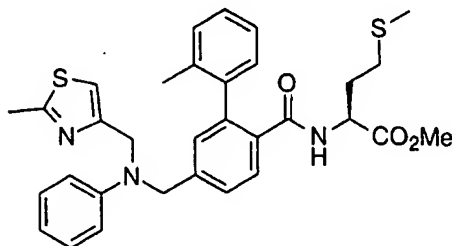
15805

Prepared according to the procedure of example 1178J from 1255A. NMR ¹H(MeOH-d₄): 7.8-7.9 (1H, m); 7.5-7.6 (1H, m), 7.42-7.45 (1H, m); 7.1-7.3 (9H, m); 6.95-7.1 (3H, m); 4.9 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 593(M-Li).



Example 1256

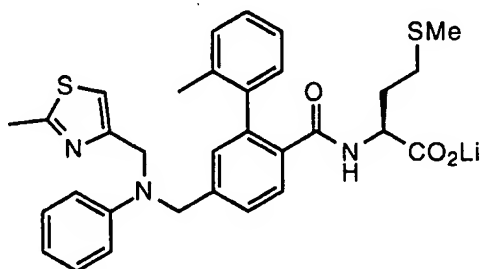
15810 *N*-[4-*N*-(*N*-phenyl-*N*-(2-methyl-4-methylenethiazolyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Example 1256A

15815 *N*-[4-*N*-(*N*-phenyl-*N*-(2-methyl-4-methylenethiazolyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1236A from reaction between 1236C and 4-methyl-2-(bromomethyl)-thiazole. NMR(CDCl₃) 7.82-7.95 (m, 1H); 7.10-7.40 (m, 9H); 6.8 (s, 1H); 6.7-6.8 (m, 2H); 5.8-5.9 (m, 1H); 4.78 (s, 2H); 4.75 (s, 2H); 4.56-4.7 (m, 1H); 3.68 (s, 3H); 2.67 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 574(M+H)⁺.

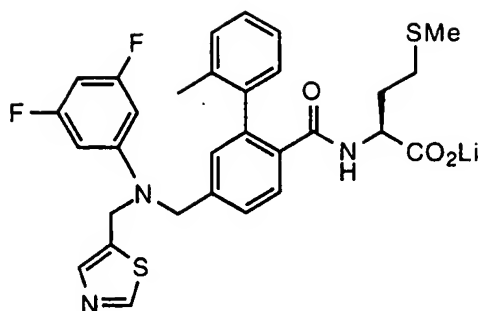
15820

Example 1256B

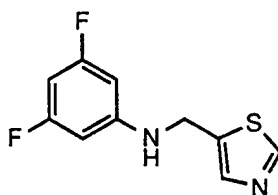
15825 *N*-[4-*N*-(*N*-phenyl-*N*-(2-methyl-4-methylenethiazolyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Prepared according to the procedure of example 1178J from 1256A. NMR ¹H(MeOH-d₄): 7.6-7.68 (1H, m); 7.32-7.4 (1H, m), 7.0-7.28 (9H, m); 6.7-6.8 (2H, m); 6.6-6.7 (1H, m); 4.78 (2H, s); 4.70 (2H, s); 4.1-4.22 (1H, m); 2.62 (3H, s); 1.7-2.1 (10H, m). ESI(-)/MS: 558(M-Li).

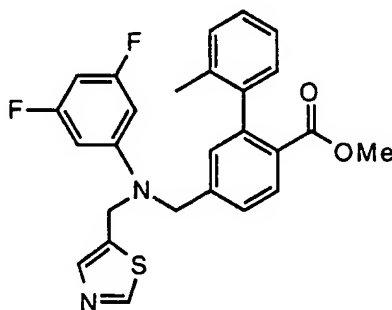
15830

Example 1257

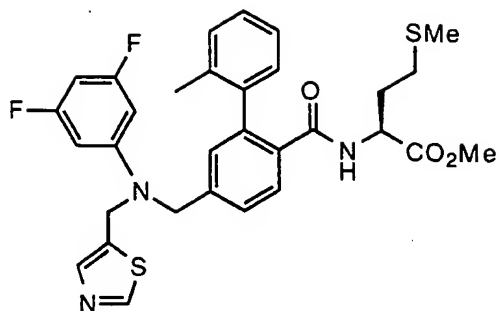
15835 N-[4-N-(N-3,5-difluorophenyl)-N-(5-thiazolylmethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

Example 1257A

15840 Prepared according to the procedure of example 1258A from reaction between 3,5-difluoroaniline and 5-thiazoalecarboxaldehyde. NMR(CDCl₃) 8.85 (s, 1H); 7.82 (s, 1H); 6.10-6.30 (m, 3H); 4.56 (s, 2H); 4.05-4.50 (m, 1H). DSI/NH₃/MS: 227(M+H)⁺; 244(M+NH₄)⁺.

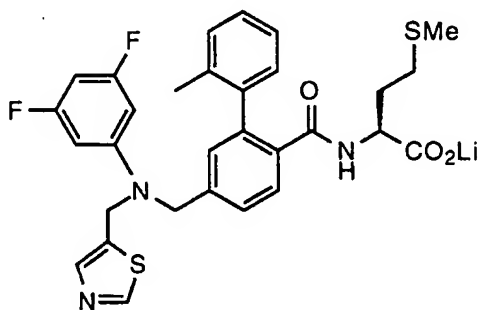
Example 1257B

15845 Prepared according to the procedure of example 1287B from reaction between 1257A and 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester. NMR(CDCl₃) 8.75-8.80 (s, 1H); 7.82-8.00 (m, 1H); 7.75 (s, 1H); 7.12-7.38 (m, 4H); 7.00-7.10 (m, 2H); 6.20-6.27 (m, 3H); 4.80 (s, 2H); 4.60 (s, 2H); 3.60 (s, 3H); 2.03 (s, 3H). DSI/NH₃/MS: 465(M+H)⁺; 482(M+NH₄)⁺.

Example 1257C

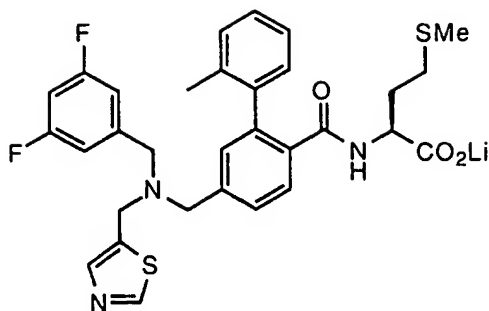
15855 N-[4-N-(N-3,5-difluorophenyl)-N-(5-thiazolylmethyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, methyl ester.

Prepared according to the procedure of example 1258C from 1257B. NMR(CDCl₃)
 8.75-8.80 (s, 1H); 7.80-7.90 (m, 1H); 7.65-7.80 (m, 1H); 7.12-7.38 (m, 5H); 6.93 (s,
 1H); 6.10-6.20 (m, 3H); 4.68 (s, 2H); 4.48-4.60 (m, 3H); 3.57 (s, 3H); 1.90-2.10 (m,
 15860 8H); 1.60-1.90 (m, 1H); 1.45-1.60 (m, 1H). DSI/NH₃/MS: 596(M+H)⁺.

Example 1257D

15865 N-[4-N-(N-3,5-difluorophenyl)-N-(5-thiazolylmethyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine lithium salt.

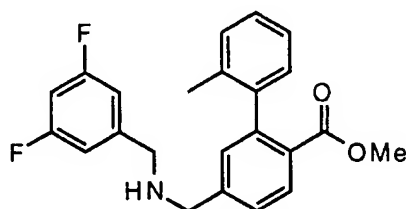
Prepared according to the procedure of example 1178J from 1257C. ¹H NMR
 (MeOH-d₄): 8.9 (1H, s); 7.8 (1H, s); 7.6-7.7 (1H, m); 7.3-7.4 (1H, m); 7.1-7.3 (3H, m);
 7.0-7.1 (1H, s); 6.3-6.45 (2H, m); 6.2-6.3 (1H, s); 4.95 (2H, s); 4.7 (2H, s); 4.1-4.22
 (1H, m); 1.6-2.2 (10H, m). ESI(-)/MS: 580(M-Li). Anal. Calcd for
 15870 C₃₀H₂₈F₂N₃O₃S₂Li•1.73H₂O: C, 58.23; H, 5.12; N, 6.79. Found: C, 58.24; H, 4.90;
 N, 6.54.



15875

Example 1258

N-[4-N-(N-(5-thiazolyl)methyl)-N-(3,5-difluorobenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt.



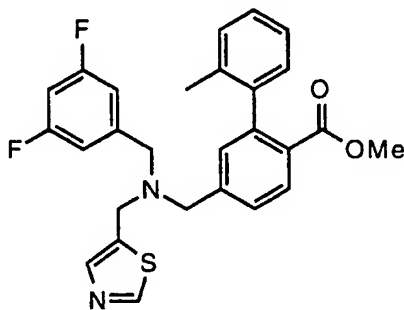
15880

Example 1258A

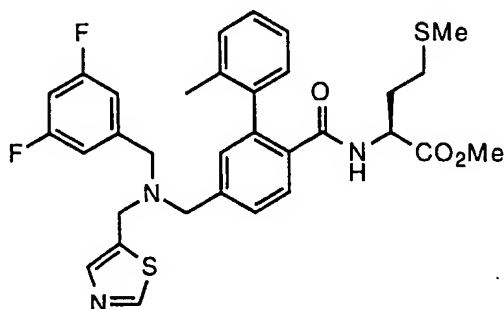
A mixture of 3,5-difluorobenzyl amine (2.0 g, 14.2 mmol), 4-formyl-2-(2-methylphenyl)benzoic acid methyl ester (3.6 g, 14.2 mmol), and sodium triacetoxyborohydride (6.0 g, 28.8 mmol) in 50 ml of 1,2-dichloroethane was stirred for 24 hours. The reaction mixture was washed with 4N NaOH and with brine, then dried over anhydrous MgSO_4 . Flash chromatography of the residue from evaporation of the organic solution eluting with 1:1 EtOAc/Hexane afforded 4.01 g of the title compound. (74%).

NMR(CDCl_3) 7.95-8.00 (m, 1H); 7.38-7.45 (m, 1H); 7.18-7.30 (m, 4H); 7.05-7.15 (m, 1H); 6.85-6.92 (m, 2H); 6.63-6.72 (m, 1H); 3.88 (s, 2H); 3.80 (s, 2H); 3.62 (s, 3H); 2.05 (s, 3H). (ESI/ NH_3)/MS: 382($\text{M}+\text{H}$)⁺; 399($\text{M}+\text{NH}_4$)⁺.

15890

Example 1258B

Prepared according to the procedure of example 1258A from reaction between 1258A and 5-thiazolealdehyde. NMR(CDCI₃) 8.80 (s, 1H); 7.95-8.00 (m, 1H); 7.72 (s, 1H); 7.50-7.55 (m, 1H); 7.10-7.32 (m, 4H); 7.0-7.1 (m, 1H); 6.9-7.0 (m, 2H); 6.68-6.72 (m, 1H); 4.62-4.70 (m, 2H); 3.60 (s, 5H); 2.07 (s, 3H). (DSI/NH₃)/MS: 479(M+H)⁺; 496(M+NH₄)⁺.

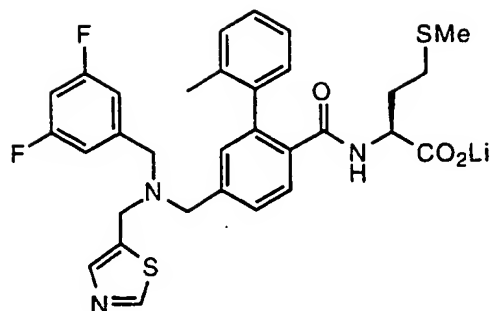


Example 1258C

A mixture of 1258B (0.304 g, 0.63 mmol) and lithium hydroxide (0.076 g, 3.15 mmol) in 30 ml of 1:1 water/methanol was refluxed for 12 hours. After cooling to room temperature, the reaction mixture was neutralized to pH= 5-6 carefully by 1.0 M NaHSO₄. The precipitate from neutralization was extracted into 40 ml of EtOAc. The organic solution was then washed by brine, and dried over anhydrous MgSO₄. Evaporation of the solvent afforded pure corresponding acid which was used directly for methionine coupling reaction.

A mixture of the acid (0.30g, 0.63 mmol) from previous step, L-methionine methyl ester hydrochloride (0.252g, 1.26 mmol), 1-hydroxybenzotriazole hydrate (0.43 g, 3.15 mmol), 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide (0.61 g, 3.15 mmol), and triethylamine hydrochloride (0.43 g, 3.15 mmol) in 15 ml of anhydrous DMF was heated under N₂ at 75°C for 20 hours. After cooling to room temperature, the solution was diluted with 50 ml of EtOAc, then was put to 200 ml of water. The aqueous solution was extracted with another portion of 50 ml of EtOAc. Combined organic solution was washed with 30 ml of saturated NaHCO₃ twice, then with 50 ml of brine, finally dried over anhydrous MgSO₄. Flash chromatography of the residue from evaporation of the EtOAc solution eluting with 70:30 EtOAc/Hexane afforded 0.235 g of the title compound. (61%).

NMR(CDCI₃) 8.78 (s, 1H); 7.90-8.00 (m, 1H); 7.72 (s, 1H); 7.50-7.55 (m, 1H); 7.20-7.38 (m, 5H); 6.9-7.0 (m, 2H); 6.68-6.72 (m, 1H); 5.88-5.92 (m, 2H); 4.58-4.70 (m, 1H); 3.88 (s, 2H); 4.62-4.70 (m, 5H); 3.60 (s, 2H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 610(M+H)⁺.



Example 1258D

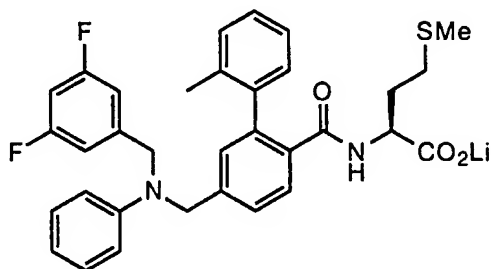
N-[4-N-(N-(5-thiazolylmethyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

15925

Prepared according to the procedure of example of 1178J from example 1258C.

NMR ^1H (MeOH- d_4): 8.95 (1H, s); 7.78 (1H, s); 7.6-7.7 (1H, m); 7.4-7.5 (1H, m), 7.05-7.3 (5H, m); 6.95-7.05(2H, m); 6.85-6.95 (1H, m); 4.95 (2H, s); 4.1-4.22 (1H, m); 3.9 (2H, s); 4.7 (2H, m); 4.6 (2H, s); 2.25 (2H, s); 1.6-2.1 (8H, m). ESI(-)/MS: 594(M-

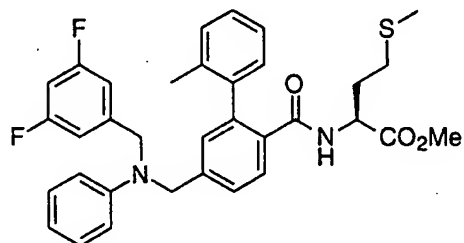
15930 Li).



Example 1259

N-[4-N-(N-phenyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

15935

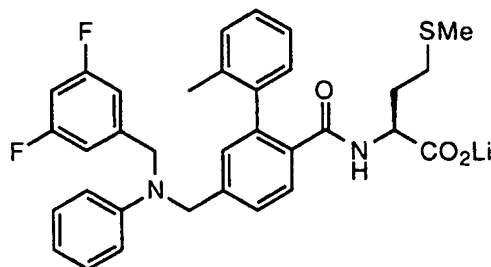


Example 1259A

N-[4-N-(N-phenyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

15940

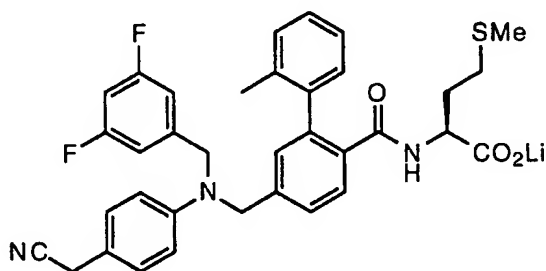
Prepared according to the procedure of example 1236A from reaction between 1236C and 3,5-difluorobenzyl bromide. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.18-7.40 (m, 9H); 7.1 (s, 1H); 6.75-6.8 (m, 2H); 6.65-6.75 (m, 2H); 5.8-5.9 (m, 1H); 4.7 (s, 2H); 4.6 (m, 3H); 3.68 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 589(M+H)⁺.



Example 1259B

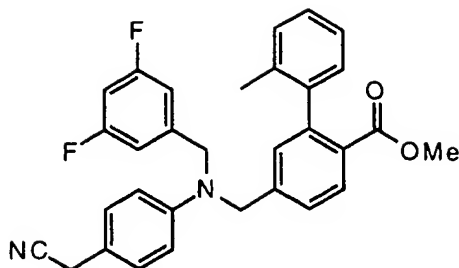
N-[4-*N*-(*N*-phenyl-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

Prepared according to the procedure of example 1178J from 1259A. NMR ¹H(MeOH-d₄): 7.7-7.8 (1H, m); 7.3-7.4 (1H, d), 7.0-7.3 (7H, d); 6.8-6.9 (3H, m); 6.6-6.8 (4H, m); 4.88 (2H, s); 4.85 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m). ESI(-)/MS: 573(M-Li).



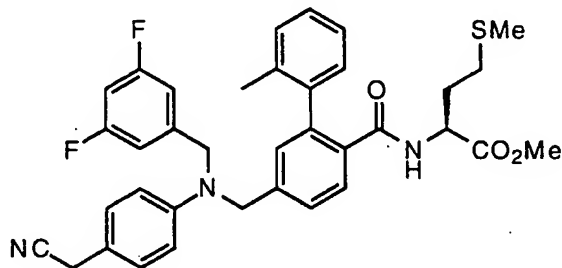
Example 1260

N-[4-*N*-(*N*-(4-acetonitrilephenyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

Example 1260A

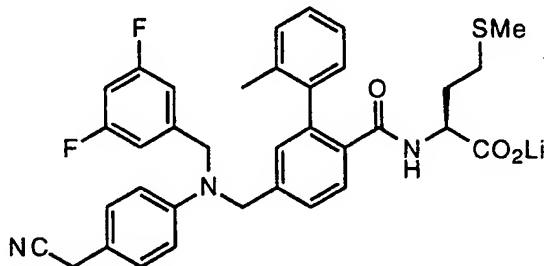
15965 Prepared according to the procedure of example 1236A from reaction 3,5-difluorobenzyl bromide, 4-bromomethyl-2-(2-methylphenyl)benzoic methyl ester, and 4-aminobenzyl cyanide. NMR(CDCl₃) 7.95-8.00 (m, 1H); 7.02-7.35 (m, 8H); 6.62-6.80 (m, 5H); 4.75 (s, 2H); 4.65 (s, 2H); 3.65 (s, 2H); 3.60 (s, 3H); 2.01 (s, 3H). (DSI/NH₃)/MS: 497(M+H)⁺; 514(M+NH₄)⁺.

15970

Example 1260B

N-[4-N-(N-(4-acetonitrilephenyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

15975 Prepared according to the procedure of example 1258C from example 1260A. NMR(CDCl₃) 7.85-7.95 (m, 1H); 7.05-7.38 (m, 7H); 7.05 (s, 1H); 6.6-6.80 (m, 5H); 5.80-5.90 (m, 1H); 4.70 (s, 2H); 4.60 (s, 2H); 3.65 (s, 2H); 3.61 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 628(M+H)⁺; 645(M+NH₄)⁺.



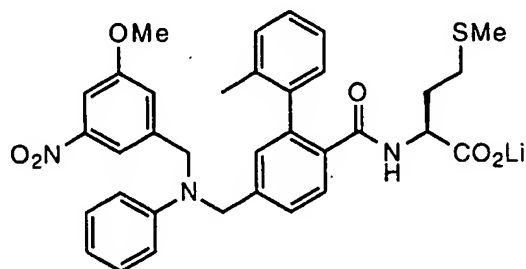
15980

Example 1260C

N-[4-N-(N-(4-acetonitrilephenyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

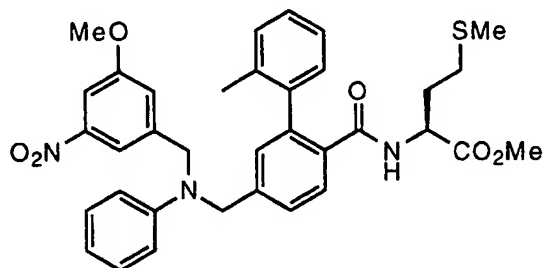
Prepared according to the procedure of example 1178J from example 1260B. NMR
 15985 ^1H (MeOH- d_4): 7.6-7.7 (1H, m); 7.3-7.4 (1H, m); 7.0-7.3 (8H, m); 6.65-6.9 (5H, m);
 4.78 (2H, s); 4.7 (3H, s); 4.1-4.22 (1H, m); 3.7 (2H, s); 1.7-2.1 (10H, m). ESI(-)/MS:
 612(M-Li). Anal. Calcd for $\text{C}_{35}\text{H}_{32}\text{F}_2\text{N}_3\text{O}_3\text{SLi} \cdot 1.64 \text{ H}_2\text{O}$: C, 64.76; H, 5.48; N, 6.47.
 Found: C, 64.75; H, 5.19; N, 6.16.

15990

Example 1261

N-[4-*N*-(*N*-phenyl-*N*-(3-methoxy-5-nitrobenzyl)aminomethyl)-2-(2-
 methylphenyl)benzoyl]methionine lithium salt.

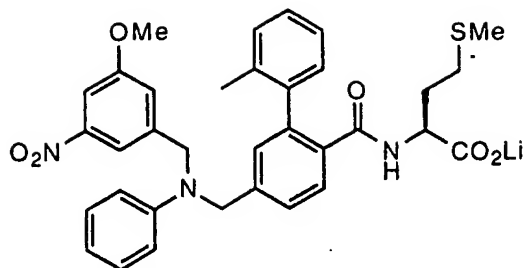
15995

Example 1261A

N-[4-*N*-(*N*-phenyl-*N*-(3-methoxy-5-nitrobenzyl)aminomethyl)-2-(2-
 methylphenyl)benzoyl]methionine, methyl ester

16000

Prepared according to the procedure of example 1236A from reaction between
 1236C and 3-methoxy-5nitrobenzyl bromide. NMR(CDCl_3) 8.1-8.2 (m, 2H); 8.0 (s, 1H);
 7.68-7.95 (m, 1H); 7.1-7.40 (m, 8H); 6.9-6.95 (m, 1H); 6.7-6.8 (m, 1H); 6.6-6.7 (m,
 2H); 5.8-5.9 (m, 1H); 4.78 (s, 2H); 4.6 (m, 3H); 3.92 (s, 3H); 3.68 (s, 3H); 2.0-2.15 (m,
 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSL/ NH_3)/MS: 628(M+H) $^+$.

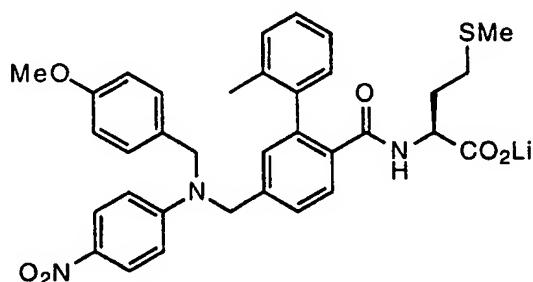


Example 1261B

N-[4-N-(N-phenyl-N-(3-methoxy-5-nitrobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

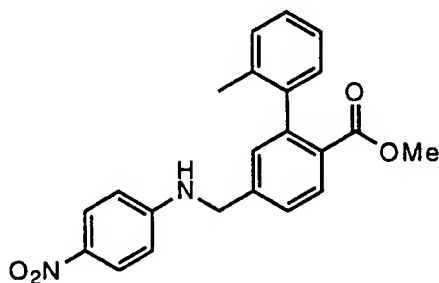
Prepared according to the procedure of example 1178J from 1261A. NMR

¹H(MeOH-d₄): 8.1-8.2 (1H, m); 7.9-8.0 (1H, m), 7.6-7.7 (1H, m); 7.3-7.4 (1H, m); 7.0-7.3 (9H, m); 6.6-6.75 (3H, m); 4.8(2H, s); 4.72 (2H, s); 4.1-4.22(1H, m); 3.95 (3H, s); 1.7-2.1 (10H, m). ESI(-)/MS: 612(M-Li).



Example 1262

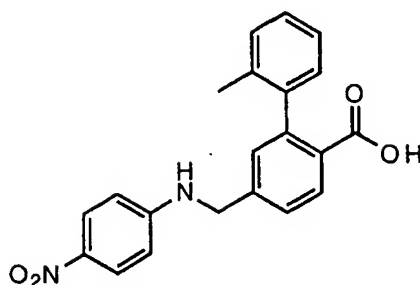
N-[4-N-(N-(4-nitrophenyl)-N-(4-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.



Example 1262A

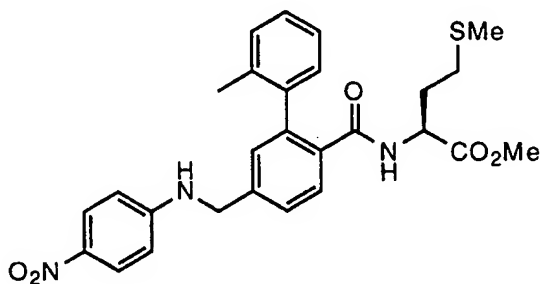
Prepared according to the procedure of example 1236A. Instead of using aniline, 4-nitroaniline was used to make the title compound. NMR(CDCl₃) 8.08-8.11 (m, 2H); 7.94-8.00 (m, 1H); 7.38-7.42 (m, 1H); 7.18-7.24 (m, 5H); 7.0-7.18 (m, 1H); 6.55-6.60 (m,

16025 2H); 4.95 (m, 1H); 4.52 (s, 2H); 3.60 (s, 3H); 2.00 (s, 3H). (DSI/NH₃)/MS: 394(M+NH₄)⁺.



Example 1262B

16030 Prepared according to the procedure of example 1178H from 1262A. NMR(CDCl₃) 8.08-8.11 (m, 2H); 7.94-8.00 (m, 1H); 7.38-7.42 (m, 1H); 7.18-7.24 (m, 5H); 7.0-7.18 (m, 1H); 6.55-6.60 (m, 2H); 4.95 (m, 1H); 4.52 (s, 2H); 2.00 (s, 3H). (DSI/NH₃)/MS: 380(M+NH₄)⁺.

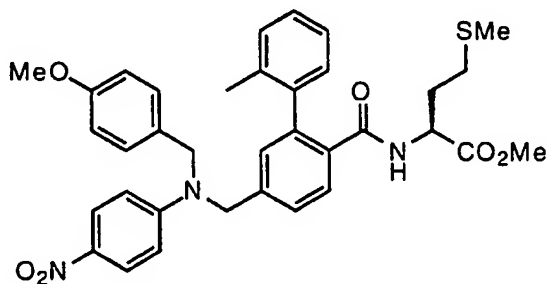


16035

Example 1262C

Prepared according to the procedure of example 1178I from 1262B. NMR(CDCl₃) 8.08-8.11 (m, 2H); 7.94-8.00 (m, 1H); 7.38-7.42 (m, 1H); 7.20-7.38 (m, 5H); 7.18-7.20 (m, 1H); 6.55-6.60 (m, 2H); 5.89-5.95 (m, 1H); 4.95-5.00 (m, 1H); 4.58-4.70 (m, 1H); 4.55 (m, 2H); 3.62 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 508(M+H)⁺; 525(M+NH₄)⁺.

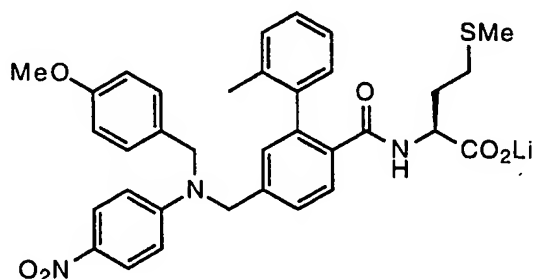
16040



Example 1262D

16045 *N*-[4-*N*-(*N*-(4-nitrophenyl)-*N*-(4-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1236A from reaction between 1262C and 4-methoxybenzyl bromide. NMR(CDCl₃) 8.08-8.11 (m, 2H); 7.94-8.00 (m, 1H); 7.38-7.42 (m, 1H); 7.11-7.40 (m, 6H); 7.00 (m, 1H); 6.85-6.95 (m, 3H); 6.55-6.60 (m, 2H); 5.89-5.95 (m, 1H); 4.80 (s, 2H); 4.70(s, 2H); 4.60-4.70 (m, 1H); 3.80 (s, 3H); 3.67 (s, 3H); 2.0-2.15 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 628(M+H)⁺.

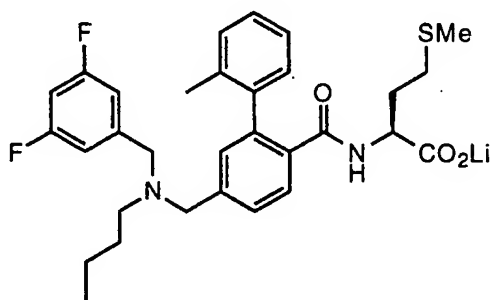


16055

Example 1262E

N-[4-*N*-(*N*-(4-nitrophenyl)-*N*-(4-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

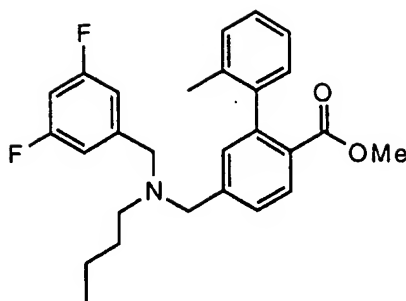
Prepared according to the procedure of example 1178J from 1262D. NMR ¹H(MeOH-d₄): 8.0-8.05 (2H, m); 7.4-7.5 (1H, m), 7.3-7.4 (1H, m); 7.18-7.3 (7H, m); 7.0 (1H, m); 6.8-6.9 (4H, m); 4.8-4.85 (4H, m); 4.1-4.22 (1H, m); 3.88 (3H, s); 1.7-2.1 (10H, m). ESI(-)/MS: 612(M-Li).



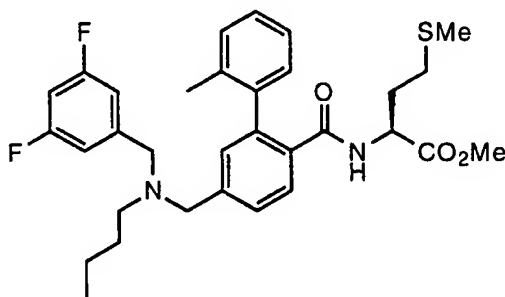
16065

Example 1263

N-[4-*N*-(*N*-butyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

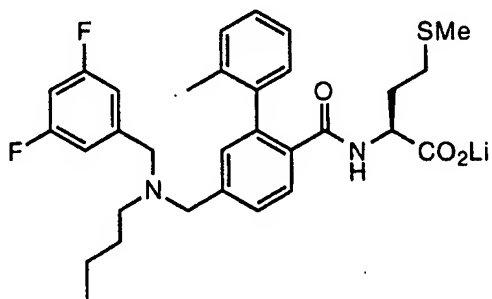
**Example 1263A**

Prepared according to the procedure of example 1258A from reaction between 1258A and butyraldehyde. NMR(CDCl₃) 7.92-7.98 (m, 1H); 7.38-7.45 (m, 1H); 7.10-7.32 (m, 4H); 7.0-7.1 (m, 1H); 6.8-6.95 (m, 2H); 6.60-6.75 (m, 1H); 3.58-3.63 (m, 5H); 3.55 (s, 2H); 2.38-2.48 (t, 2H); 2.07 (s, 3H); 1.4-1.6 (m, 2H); 1.2-1.4 (m, 2H); 0.8-0.9 (t, 3H). (DSI/NH₃)/MS: 437(M+H)⁺.

**Example 1263B**

N-[4-N-(N-butyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1258C from 1263A. NMR(CDCl₃) 7.9-8.00 (m, 1H); 7.40-7.46 (m, 1H); 7.20-7.40 (m, 4H); 7.20 (s, 1H); 6.7-6.85 (m, 2H); 6.60-6.75 (m, 1H); 5.82-5.92 (m, 1H); 4.58-4.70 (m, 1H); 3.65 (s, 3H); 3.60 (s, 2H); 3.55 (s, 2H); 2.40-2.48 (t, 2H); 2.20 (s, 3H); 1.8-1.96(m, 1H); 1.55-1.65 (m, 1H); 1.45-1.55 (m, 2H); 1.2-1.4 (m, 2H); 0.8-0.9 (t, 3H). (DSI/NH₃)/MS: 569(M+H)⁺.



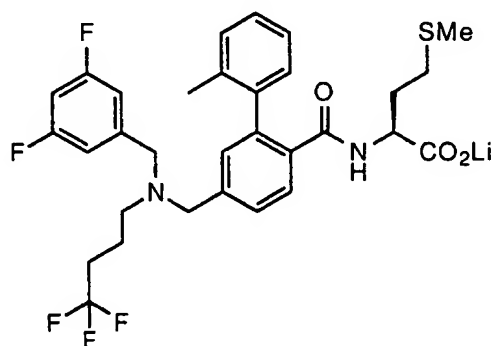
Example 1263C

N-[4-*N*-(*N*-butyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

16090

Prepared according to the procedure of example 1178J from 1263B. NMR ^1H (MeOH- d_4): 7.6-7.7 (1H, m); 7.4-7.48 (1H, m), 7.0-7.28 (6H, m); 6.9-7.0 (2H, m); 6.7-6.8 (1H, m); 4.1-4.22 (1H, m); 3.65 (2H, s); 3.58 (2H, s); 2.4-2.5 (2H, m); 2.21 (1H, m); 1.8-2.1 (10H, m); 1.4-1.5 (2H, m); 1.22-1.4 (2H, m); 0.8-0.9 (3H, m). ESI(-)/MS: 553(M-Li). Anal. Calcd for $\text{C}_{31}\text{H}_{35}\text{F}_2\text{N}_2\text{O}_3\text{SLi} \cdot 1.5 \text{ LiOH} \cdot 0.26\text{H}_2\text{O}$: C, 62.04; H, 6.05; N, 4.48. Found: C, 62.04; H, 6.05; N, 4.67.

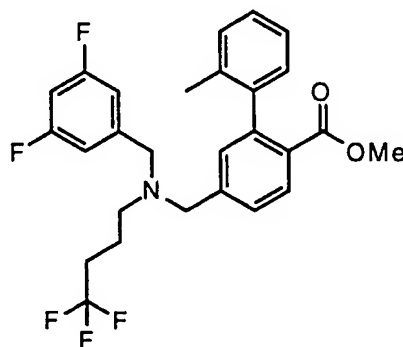
16095



16100

Example 1264

N-[4-*N*-(*N*-(4,4,4-trifluorobutyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

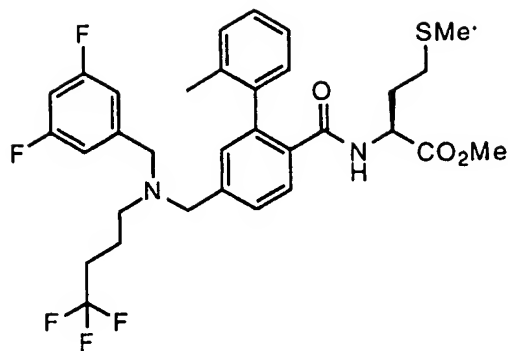


16105

Example 1264A

Prepared according to the procedure of example 1258A from reaction between 1258A and 4,4,4-trifluorobutylaldehyde. NMR(CDCl_3) 7.92-7.98 (m, 1H); 7.38-7.45 (m, 1H); 7.10-7.32 (m, 4H); 7.0-7.1 (m, 1H); 6.8-6.92 (m, 2H); 6.62-6.78 (m, 1H); 3.58-3.63 (m, 5H); 3.55 (s, 2H); 2.43-2.55 (t, 2H); 2.00-2.1 (m, 5H); 1.7-1.82 (m, 2H). (DSI/ NH_3)/MS: 492(M+H) $^+$.

16110

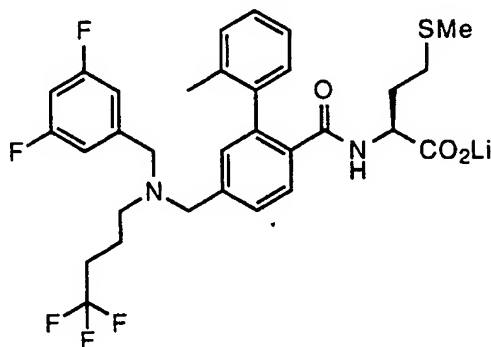
Example 1264B

N-[4-N-(N-(4,4,4-trifluorobutyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

16115

Prepared according to the procedure of example 1258C from 1264A. NMR(CDCl₃) 7.9-8.00 (m, 1H); 7.40-7.46 (m, 1H); 7.20-7.40 (m, 4H); 7.20 (s, 1H); 6.7-6.85 (m, 2H); 6.60-6.75 (m, 1H); 5.82-5.92 (m, 1H); 4.58-4.70 (m, 1H); 3.65 (s, 3H); 3.61 (s, 2H); 3.55 (s, 2H); 2.40-2.48 (t, 2H); 1.5-2.16 (m, 14H). (DSI/NH₃)/MS: 623(M+H)⁺.

16120

Example 1264C

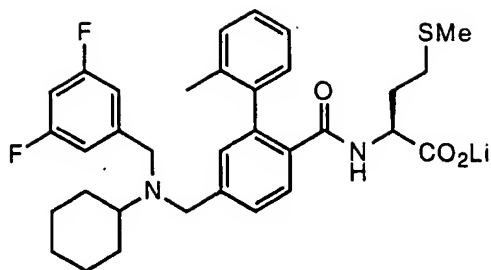
N-[4-N-(N-(4,4,4-trifluorobutyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

16125

Prepared according to the procedure of example 1178J from 1264B. NMR ¹H(MeOH-d₄): 7.6-7.7 (1H, m); 7.4-7.48 (1H, m), 7.0-7.28 (6H, m); 6.9-7.0 (2H, m); 6.7-6.8 (1H, m); 4.1-4.22 (1H, m); 3.65 (2H, s); 3.6 (2H, s); 2.5-2.6 (2H, m); 1.6-2.25 (14H, m); 1.4-1.5 (2H, m); 1.22-1.4 (2H, m); 0.8-0.9 (3H, m). ESI(-)/MS: 609(M-Li). Anal. Calcd for C₃₁H₃₀F₅N₂O₃SLi•1.21H₂O: C, 58.70; H, 5.15; N, 4.42. Found: C,

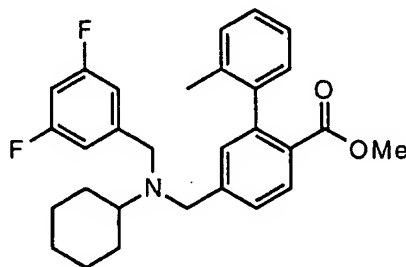
16130

58.69; H, 5.16; N, 4.18.

Example 1265

16135

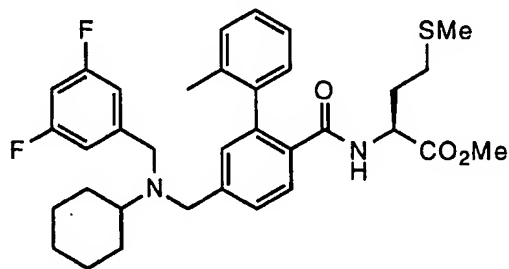
N-[4-*N*-(*N*-cyclohexyl-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

Example 1265A.

16140

Prepared according to the procedure of example 1258A from reaction between 1258A and cyclohexanone. NMR (CDCl₃) 7.90-7.95 (m, 1H); 7.40-7.45 (m, 1H); 7.18-7.38 (m, 4H); 7.00-7.09 (m, 1H); 6.84-6.94 (m, 2H); 6.58-6.68 (m, 1H); 3.68 (s, 2H); 3.62 (m, 5H); 2.40-2.50 (m, 1H); 2.08 (s, 3H); 1.75-1.96 (m, 4H); 1.05-1.65 (m, 6H). (DSI/NH₃)/MS: 464(M+H)⁺.

16145

Example 1265B

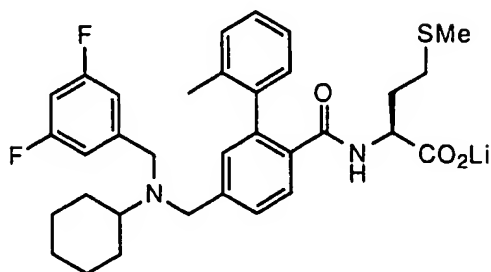
N-[4-*N*-(*N*-cyclohexyl-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

16150

Prepared according to the procedure of example 1258C from 1265A. NMR (CDCl₃) 7.85-7.95 (m, 1H); 7.38-7.45 (m, 1H); 7.18-7.38 (m, 4H); 7.2 (s, 1H); 6.84-6.94 (m, 2H); 6.58-6.68 (m, 1H); 5.85-5.93 (m, 1H); 4.56-4.65 (m, 1H); 3.70 (s, 2H); 3.65 (s,

2H); 3.61 (s, 3H); 2.40-2.50 (m, 1H); 1.96-2.18 (m, 7H); 1.71-1.96 (m, 6H); 1.55-1.68 (m, 1H); 1.05-1.52 (m, 6H). (DSI/NH₃)/MS: 595(M+H)⁺.

16155

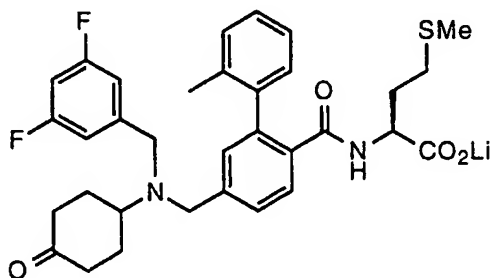
Example 1265C

N-[4-N-(N-cyclohexyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

16160

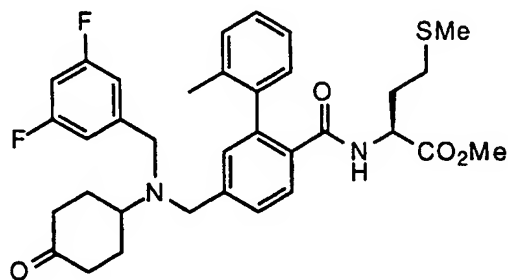
Prepared according to the procedure of example 1178J from 1265B. NMR ¹H(MeOH-d₄): 7.6-7.7 (1H, m); 7.35-7.45 (1H, m), 7.0-7.35 (5H, m); 6.9-7.0 (2H, m); 6.7-6.8 (1H, m); 4.1-4.22 (1H, m); 3.7 (3H, s); 3.65 (3H, s); 2.4-2.52 (1H, m); 2.1 (1H, m); 1.7-2.1 (11H, m); 1.5-1.7 (2H, m); 1.23-1.5 (2H, m); 1.05-1.25 (3H, m). ESI(-)/MS: 579(M-Li).

16165

Example 1266

N-[4-N-(N-(4-cyclohexanonyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

16170

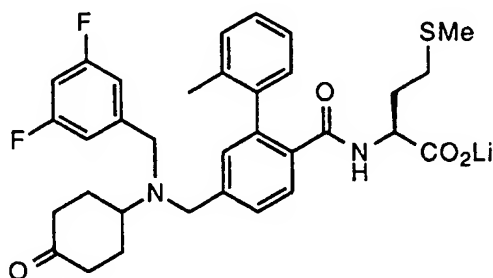
Example 1266A

N-[4-*N*-(*N*-(4-cyclohexanonyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

16175

A mixture of 1267B (0.42 g, 0.604 mmol) and 10 ml of 10% of HCl in 35 ml of acetone was refluxed until all 1267B disappeared. Solvents were removed under vacuum. The residue was treated with 20 ml of 2N Na₂CO₃, then extracted by 50 ml of EtOAc. The organic solution was then washed with brine, dried over anhydrous MgSO₄. The crude product was purified by flash chromatography eluting with 1:1 EtOAc/Hexane to afford 0.25 g of the title compound. NMR (CDCl₃) 7.82-7.95 (m, 1H); 7.40-7.49 (m, 1H); 7.18-7.40 (m, 5H); 6.82-6.92 (m, 2H); 6.58-6.68 (m, 1H); 5.82-5.91 (m, 1H); 4.58-4.68 (m, 1H); 3.61-3.75 (m, 7H); 2.95-3.05 (m, 1H); 1.5-2.5 (m, 18H). (DSI/NH₃)/MS: 609(M+H)⁺; 626(M+NH₄)⁺.

16185



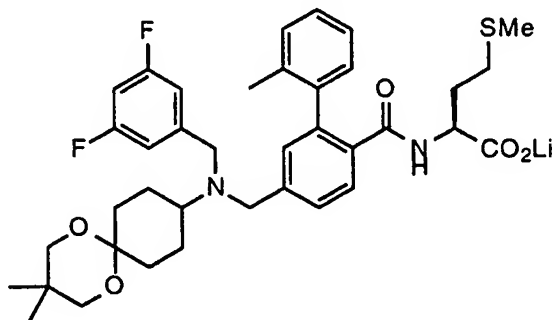
Example 1266B

N-[4-*N*-(*N*-(4-cyclohexanonyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

16190

Prepared according to the procedure of example 1178J from 1266A. NMR ¹H(MeOH-d₄): 7.6-7.7 (1H, m); 7.4-7.5 (1H, m), 7.0-7.28 (6H, m); 6.9-7.0 (2H, m); 6.7-6.8 (1H, m); 4.1-4.22 (1H, m); 3.75 (2H, s); 3.7 (2H, s); 2.1-2.3 (3H, m); 1.76-2.1 (14H, m); 1.5-1.78 (2H, m). ESI(-)/MS: 593(M-Li). Anal. Calcd for C₃₃H₃₅F₂N₂O₄SLi•1.73H₂O•1.5LiOH: C, 60.32; H, 5.95; N, 4.26. Found: C, 60.33; H, 5.62; N, 4.04.

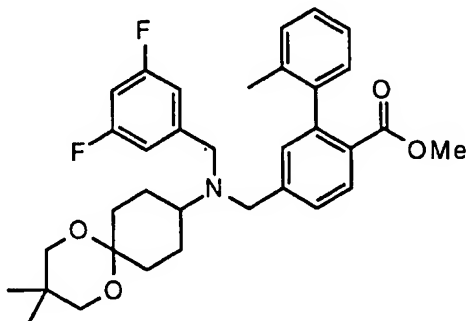
16195



.. Example 1267

16200

N-[4-*N*-(*N*-(4-(2,2-dimethyltrimethylene ketal)-cyclohexyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

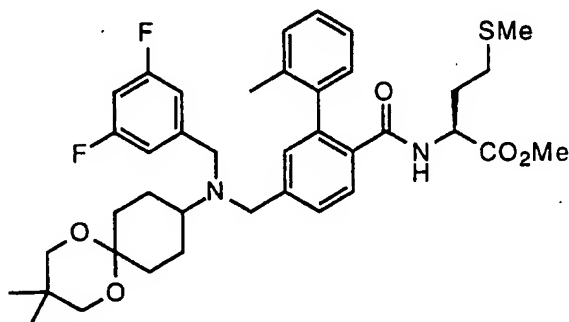


Example 1267A

16205

Prepared according to the procedure of example 1258A from reaction between 1258A and 1,4-cyclohexanedione *mono*-2,2-dimethyltrimethylene ketal. NMR (CDCl₃) 7.82-7.92 (m, 1H); 7.36-7.42 (m, 1H); 7.18-7.38 (m, 4H); 7.20 (s, 1H); 6.82-6.92 (m, 2H); 6.58-6.68 (m, 1H); 3.68 (s, 2H); 3.60 (s, 3H); 3.59 (s, 2H); 3.48 (s, 2H); 3.42 (s, 2H); 2.50-2.60 (m, 1H); 2.22-2.38 (m, 2H); 1.80-2.20 (m, 6H); 1.2-1.3 (m, 2H); 0.95 (s, 6H). (DSI/NH₃)/MS: 564(M+H)⁺.

16210



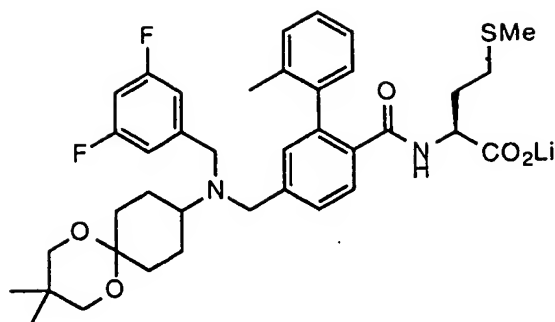
Example 1267B

16215

N-[4-*N*-(*N*-(4-(2,2-dimethyltrimethylene ketal)-cyclohexyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

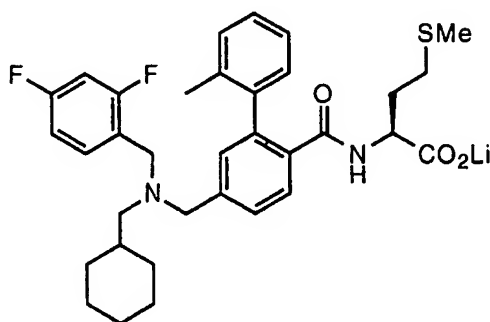
Prepared according to the procedure of example 1258C from 1267A. NMR (CDCl₃) 7.82-7.92 (m, 1H); 7.36-7.42 (m, 1H); 7.18-7.38 (m, 4H); 7.20 (s, 1H); 6.82-6.92 (m, 2H); 6.58-6.68 (m, 1H); 5.82-5.91 (m, 1H); 4.58-4.68 (m, 1H); 3.68 (s, 2H); 3.60 (s, 3H); 3.59 (s, 2H); 3.48 (s, 2H); 3.42 (s, 2H); 2.50-2.60 (m, 1H); 2.22-2.38 (m, 2H); 1.50-2.2 (m, 14H); 1.2-1.3 (m, 2H); 0.95 (s, 6H). (DSI/NH₃)/MS: 695(M+H)⁺.

16220

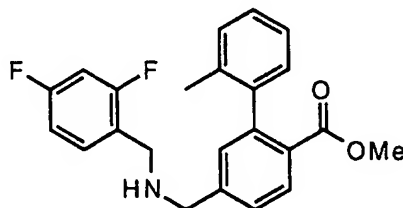
Example 1267C

16225 *N*-[4-*N*-(*N*-(4-(2,2-dimethyltrimethylene ketal)-cyclohexyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

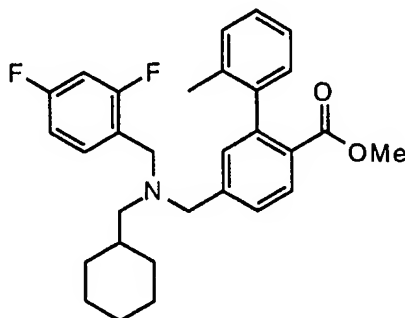
Prepared according to the procedure of example 1178J from 1267B. NMR ¹H(MeOH-d₄): 7.55-7.65 (1H, m); 7.38-7.48 (1H, m), 7.0-7.35 (6H, m); 6.9-7.0 (2H, m); 6.7-6.8 (1H, m); 4.1-4.22 (1H, m); 3.7 (2H, s); 3.65(2H, s); 3.45 (4H, s); 2.5-2.65 (1H, m); 2.26-2.4 (2H, m); 2.2 (1H, s); 1.5-2.1 (13H, m); 1.1-1.3 (2H, m); 0.95 (6H, s).
 16230 ESI(-)/MS: 686.79(M-Li). Anal. Calcd for C₃₈H₄₅F₂N₂O₅SLi•0.99H₂O•1.0LiOH: C, 62.65; H, 6.64; N, 3.84. Found: C, 62.65; H, 6.33; N, 3.71.

Example 1268

N-[4-*N*-(*N*-cyclohexylmethyl)-*N*-(2,4-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

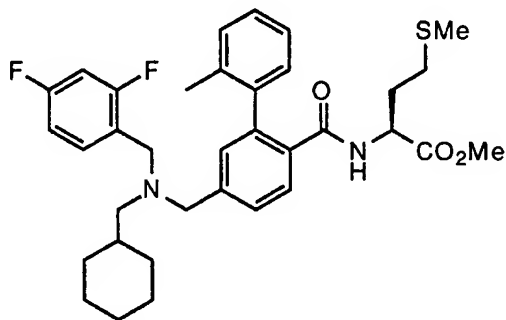
Example 1268A

Prepared according to the procedure of example 1258A from the reaction between 2,4-difluorobenzyl amine and 4-formyl-2-(2-methylphenyl)benzoic acid methyl ester. NMR (CDCl₃) 7.22-7.30 (m, 2H); 6.85-6.90 (m, 3H); 3.88 (s, 2H); 2.40-2.45 (m, 2H); 1.6-1.8 (m, 5H); 1.38-1.60 (m, 2H); 1.05-1.40 (m, 3H); 0.8-1.0 (m, 2H). (DSI/NH₃)/MS: 240(M+H)⁺.



Example 1268B

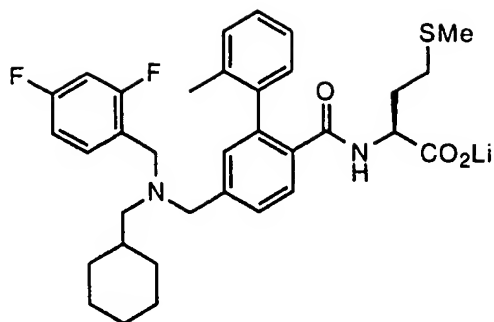
Prepared according to the procedure of example 1258A from reaction between 1268A and cyclohexanecarboxaldehyde. NMR (CDCl₃) 7.90-7.95 (m, 1H); 7.38-7.47 (m, 2H); 7.20-7.35 (m, 4H); 7.0-7.10 (m, 1H); 6.75-6.85 (m, 2H); 3.60(s, 3H); 3.55 (s, 2H); 3.52 (s, 2H); 2.20-2.23 (m, 2H); 2.05 (s, 3H); 1.72-1.83 (m, 2H); 1.52-1.72 (m, 4H); 1.10-1.30 (m, 3H); 0.6-0.8 (m, 2H). (DSI/NH₃)/MS: 478(M+H)⁺.



Example 1268C

N-[4-*N*-(*N*-cyclohexylmethyl)-*N*-(2,4-difluorobenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

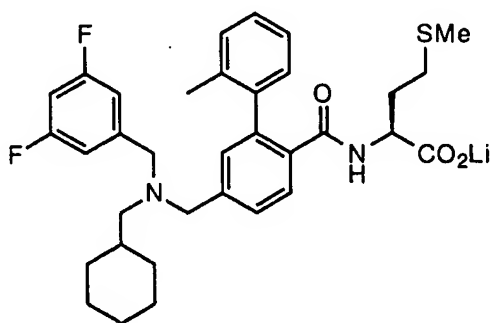
Prepared according to the procedure of example 1258C from 1268B. NMR (CDCl₃) 7.85-7.95 (m, 1H); 7.20-7.47 (m, 6H); 7.18 (s, 1H); 6.75-6.85 (m, 2H); 5.85-5.92 (m, 1H); 4.56-4.67 (m, 1H); 3.67(s, 3H); 3.57 (s, 2H); 3.55 (s, 2H); 2.18-2.23 (m, 4H); 2.00-2.11 (m, 6H); 1.72-1.83 (m, 3H); 1.52-1.72 (m, 4H); 1.10-1.30 (m, 3H); 0.6-0.8 (m, 2H). (DSI/NH₃)/MS: 609(M+H)⁺.

Example 1268D

N-[4-N-(N-cyclohexylmethyl)-N-(2,4-difluorobenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt.

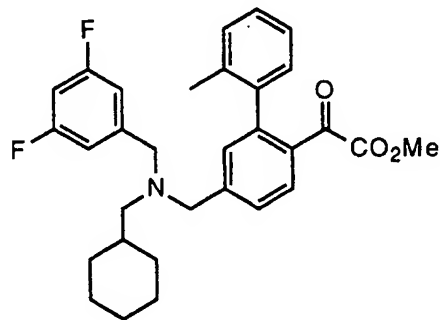
16270 Prepared according to the procedure of example 1178J from 1267C. NMR $^1\text{H}(\text{MeOH}-d_4)$: 7.6-7.7 (1H, m); 7.38-7.48 (2H, m), 7.0-7.28 (6H, m); 6.8-6.95 (2H, m); 4.1-4.22 (1H, m); 4.58 (4H, s); 2.2-2.3 (4H, m); 1.76-2.1 (9H, m); 1.5-1.78 (5H, m); 1.1-1.3 (3H, m); 0.7-0.82 (2H, m). ESI(-)/MS: 593(M-Li).

16275

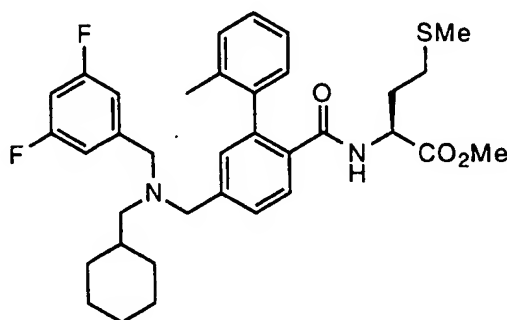
Example 1269

N-[4-N-(N-cyclohexylmethyl)-N-(3,5-difluorobenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt.

16280

Example 1269A

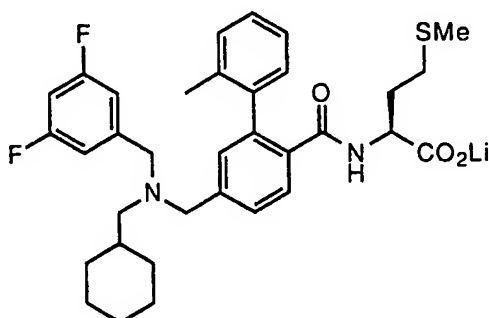
Prepared according to the procedure of example 1258A from reaction between 1258A and cyclohexanecarboxaldehyde. NMR (CDCl₃) 7.95-8.05 (m, 1H); 7.40-7.47 (m, 1H); 7.15-7.35 (m, 5H); 7.04-7.11 (m, 1H); 6.75-6.85 (m, 2H); 6.60-6.70 (m, 1H); 3.60(s, 3H); 3.55 (s, 2H); 3.45 (s, 2H); 2.18-2.25 (m, 2H); 2.05 (s, 3H); 1.72-1.83 (m, 2H); 1.52-1.72 (m, 4H); 1.10-1.30 (m, 3H); 0.6-0.8 (m, 2H). (DSI/NH₃)/MS: 478(M+H)⁺.



Example 1269B

N-[4-N-(N-cyclohexylmethyl)-N-(3,5-difluorobenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1258C from 1269A. NMR (CDCl₃) 7.79-7.95 (m, 1H); 7.40-7.48 (m, 1H); 7.20-7.41 (m, 5H); 7.18 (s, 1H); 6.75-6.85 (m, 2H); 6.60-6.70 (m, 1H); 5.85-5.92 (m, 1H); 4.56-4.67 (m, 1H); 3.67(s, 3H); 3.57 (s, 2H); 3.45 (s, 2H); 2.18-2.23 (m, 4H); 2.00-2.11 (m, 6H); 1.72-1.83 (m, 3H); 1.52-1.72 (m, 4H); 1.10-1.30 (m, 3H); 0.6-0.8 (m, 2H). (DSI/NH₃)/MS: 609(M+H)⁺.



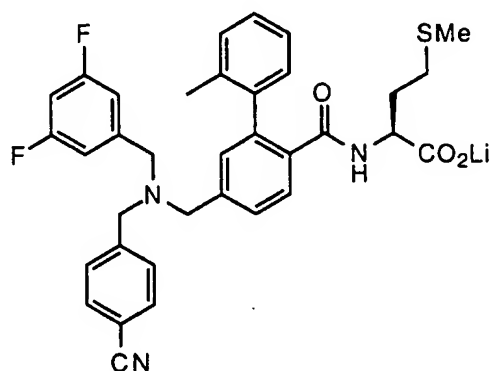
Example 1269C

N-[4-N-(N-cyclohexylmethyl)-N-(3,5-difluorobenzyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt.

Prepared according to the procedure of example 1178J from 1269B. NMR ¹H(MeOH-d₄): 7.6-7.7 (1H, m); 7.38-7.48 (1H, m), 7.0-7.28 (6H, m); 6.9-7.0 (2H, m); 6.7-6.8 (1H, m); 4.1-4.22 (1H, m); 4.6 (2H, s); 4.55 (2H, s); 2.2-2.3 (4H, m); 1.76-2.1

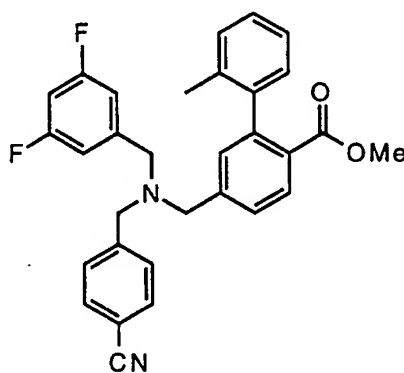
(9H, m); 1.5-1.78 (5H, m); 1.1-1.3 (3H, m); 0.7-0.82 (2H, m). ESI(-)/MS: 593(M-Li).
 Anal. Calcd for $C_{31}H_{30}F_5N_2O_3SLi \cdot 1.0LiOH$: C, 65.38; H, 6.45; N, 4.48 Found: C, 65.43; H, 6.17; N, 4.40.

16310

Example 1270

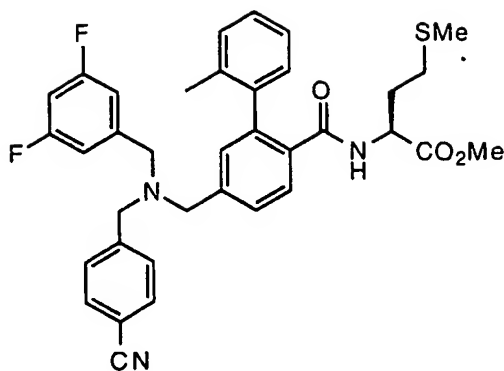
N-[4-N-(N-(4-cyanobenzyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

16315

Example 1270A

Prepared according to the procedure of example 1258A from reaction between
 1258A and 4-cyanobenzaldehyde. NMR(CDCl₃) 7.95-8.00 (m, 1H); 7.60-7.65 (m, 2H);
 7.40-7.56 (m, 3H); 7.20-7.38 (m, 4H); 7.00-7.10 (m, 1H); 6.85-6.95 (m, 2H); 6.65-6.75
 (, 1H); 3.58-3.65 (m, 7H); 3.54-3.58 (m, 2H); 2.05 (s, 3H). (DSI/NH₃)/MS: 585(M+H)+
 ; 497 (M+NH₄)+. 514 (M+NH₄)+.

16320

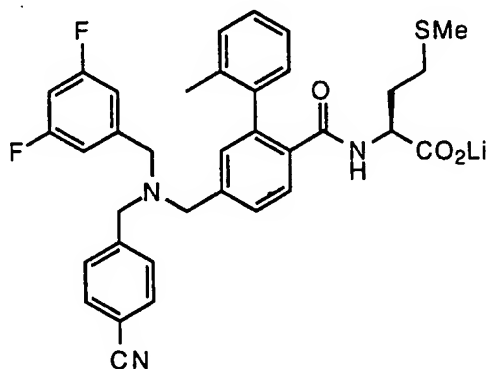


Example 1270B

N-[4-N-(N-(4-cyanobenzyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1258C from 1270A. NMR(CDCl₃)

16330 8.00-8.18 (m, 1H); 7.76-7.80 (m, 2H); 7.48-7.76 (m, 3H); 7.10-7.38 (m, 5H); 7.00-7.11 (m, 2H); 6.80-6.85 (m, 1H); 5.95-6.05 (m, 1H); 4.70-4.81 (m, 1H); 3.70-3.90 (m, 9H); 3.54-3.58 (m, 2H); 1.95-2.20 (m, 8H); 1.7-2.0 (m, 1H); 1.5-1.7 (m, 1H). (DSI/NH₃)/MS: 628(M+H)⁺; 645(M+NH₄)⁺.

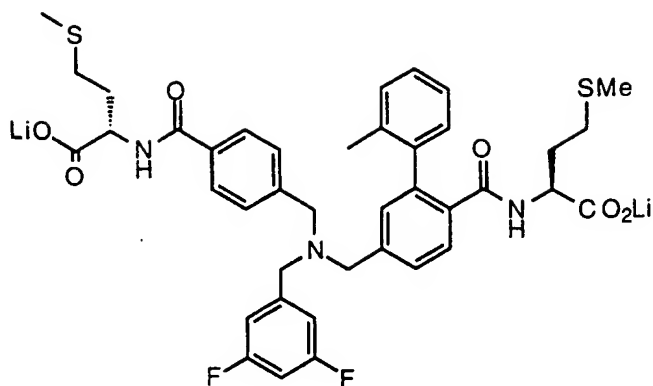


Example 1270C

N-[4-N-(N-(4-cyanobenzyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

Prepared according to the procedure of example 1178J from 1270B. NMR

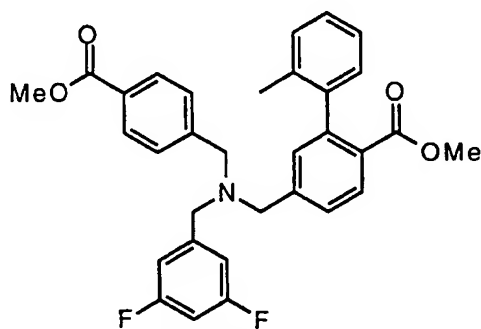
16340 ¹H(MeOH-d₄): 8.78 (1H, s); 7.6-7.7 (2H, m); 7.5-7.6 (2H, m), 7.5-7.55 (1H, m); 7.0-7.3 (6H, m); 6.9-7.0 (2H, m); 6.77-6.82 (1H, m); 4.1-4.22 (1H, m); 3.7 (2H, s); 3.65 (2H, s); 3.6 (2H, s); 1.5-2.2 (10H, m).ESI(-)/MS: 612(M-Li).



16345

Example 1271

N-[4-N-(N-(3,5-difluorobenzyl)-N-(4-N-carboxymethionine)benzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine dilithium salt.

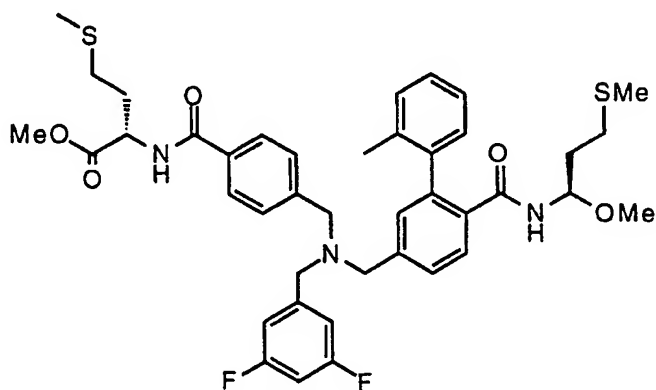


16350

Example 1271A

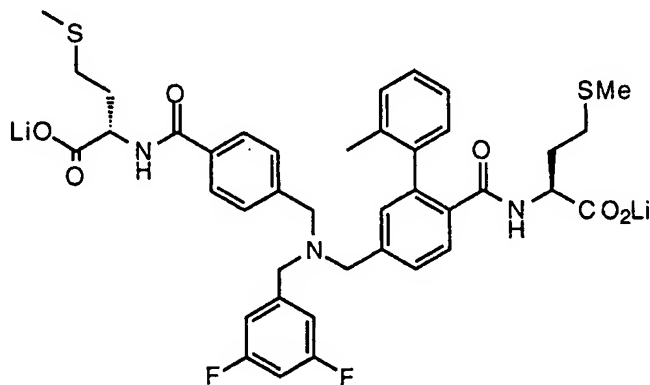
Prepared according to the procedure of example 1236A from reaction between 1258A and 4-bromomethyl-benzoic methyl ester. NMR(CDCl₃) 7.75-7.90 (m, 1H); 7.75-7.85 (m, 2H); 7.40-7.50 (m, 2H); 7.20-7.40 (m, 5H); 7.18 (s, 1H); 6.88-6.95 (m, 2H); 6.70-6.80 (m, 1H); 5.85-5.95 (m, 1H); 4.58-4.70 (m, 1H); 3.80 (s, 3H); 3.65 (s, 3H); 3.60 (s, 2H); 3.55 (s, 2H). (DSI/NH₃)/MS: 530(M+H)⁺.

16355

Example 1271B

16360 *N*-[4-*N*-(*N*-(3,5-difluorobenzyl)-*N*-(4-*N*-carboxymethionine)benzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine dimethyl ester.

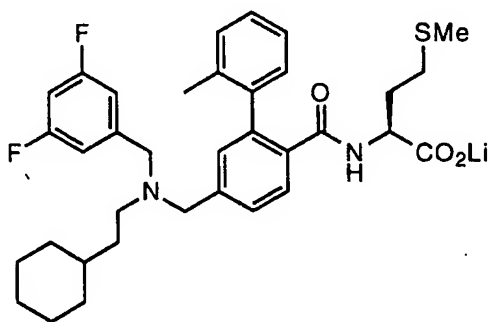
Prepared according to the procedure of example 1258C from 1271A. NMR(CDCl₃) 7.75-7.90 (m, 1H); 7.75-7.85 (m, 2H); 7.40-7.50 (m, 2H); 7.20-7.40 (m, 5H); 7.18 (s, 1H); 6.88-6.95 (m, 3H); 6.70-6.80 (m, 1H); 5.85-5.95 (m, 1H); 4.90-4.95 (m, 1H); 4.58-4.70 (m, 1H); 3.80 (s, 3H); 3.65 (s, 3H); 3.60 (s, 2H); 3.55 (s, 2H); 2.58-2.70 (m, 2H); 2.0-2.15 (m, 10H); 1.7-2.0 (m, 3H); 1.5-1.7 (m, 2H). (DSI/NH₃)/MS: 792(M+H)⁺.



Example 1271C

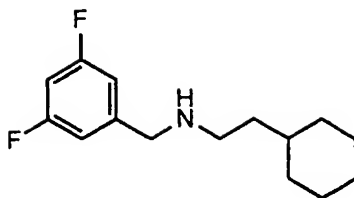
16370 *N*-[4-*N*-(*N*-(3,5-difluorobenzyl)-*N*-(4-*N*-carboxymethionine)benzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine dilithium salt.

Prepared according to the procedure of example 1178J from 1271B. NMR ¹H (d₄-MeOH): 7.8-7.9 (2H, m); 7.6-7.7 (1H, m); 7.45-7.55 (4H, m); 7.1-7.3 (6H, m); 6.9-7.05 (2H, m); 6.75-6.85 (1H, m); 4.5-4.6 (1H, m); 4.2-4.3 (1H, m); 3.4-3.5 (6H, m); 2.5-2.6 (2H, m); 1.5-2.3 (15H, m). ESI(-)/MS: 762 (M-Li); 764(M+H); 781(M+NH₄).

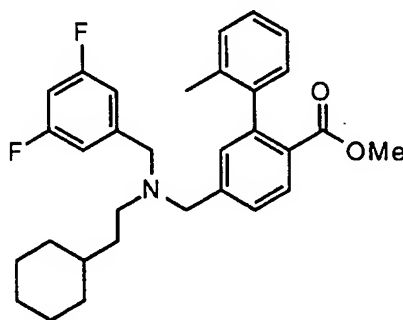


Example 1272

16380 *N*-[4-*N*-(*N*-(2-cyclohexylethyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

Example 1272A

16385 Prepared according to the procedure of example 1258A from reaction between 3,5-difluorobenzaldehyde and 2-cyclohexylethyl-1-aminoethane. NMR(CDCl₃) 6.78-6.95 (m, 2H); 6.65-6.80 (m, 3H); 3.78 (s, 2H); 2.58-2.68 (m, 2H); 1.00-1.75 (m, 11H); 0.8-1.0- (m, 2H). (DSI/NH₃)/MS: 254(M+H)⁺; 271(M+NH₄)⁺.

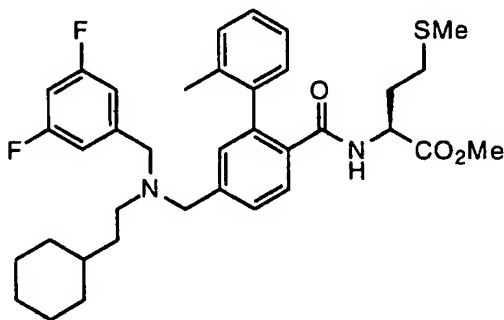


16390

Example 1272B

Prepared according to the procedure of example 1226A from the reaction between 1272A and 4-Bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester. NMR(CDCl₃) 7.91-7.98 (m, 1H); 7.38-7.45 (m, 1H); 7.10-7.30 (m, 4H); 7.05-7.15 (m, 1H); 6.83-6.95 (m, 2H); 6.60-6.78 (m, 1H); 3.60 (s, 5H); 3.55 (s, 2H); 2.40-2.50 (m, 2H); 2.05 (s, 3H); 1.50-1.75 (m, 5H); 1.30-1.47 (m, 2H); 1.00-1.38 (m, 4H); 0.74-0.90 (m, 2H). (DSI/NH₃)/MS: 492(M+H)⁺.

16395

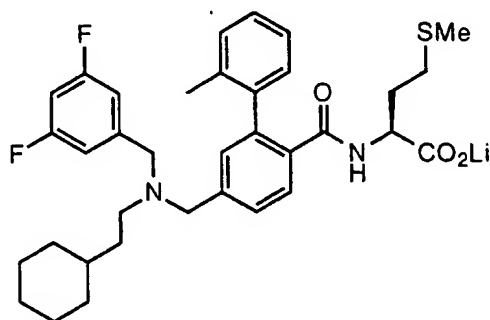


16400

Example 1272C

N-[4-N-(N-(2-cyclohexylethyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

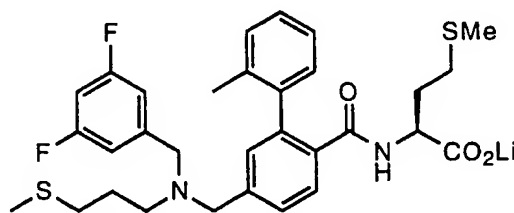
Prepared according to the procedure of example 1258C from 1272B. NMR(CDCl₃)
 7.81-7.98 (m, 1H); 7.38-7.45 (m, 2H); 7.20-7.40 (m, 3H); 7.18 (s, 1H); 6.83-6.95 (m,
 2H); 6.60-6.78 (m, 1H); 5.81-5.90 (m, 1H); 4.58-4.70 (m, 1H); 3.67 (s, 3H); 3.60 (s,
 2H); 3.55 (s, 2H); 2.40-2.50 (m, 2H); 2.00-2.20 (m, 8H); 1.70-2.00 (m, 1H); 1.50-1.70
 (m, 5H); 1.30-1.50 (m, 2H); 1.10-1.38 (m, 4H); 0.74-0.90 (m, 2H). (ESI/NH₃)/MS:
 623(M+H)⁺.



Example 1272D

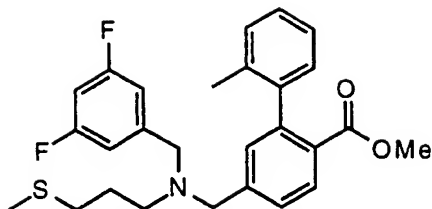
N-[4-N-(N-(2-cyclohexylethyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

Prepared according to the procedure of example 1178J from 1272C. NMR
¹H(MeOH-d₄): 7.6-7.7 (1H, m); 7.4-7.48 (1H, m), 7.0-7.28 (6H, m); 6.9-7.0 (2H, m);
 6.7-6.8 (1H, m); 4.1-4.22 (1H, m); 3.65 (2H, s); 3.58 (2H, s); 2.4-2.5 (2H, m); 2.21
 (1H, m); 1.1-2.1 (20H, m); 0.8-0.9 (2H, m). ESI(-)/MS: 607(M-Li).

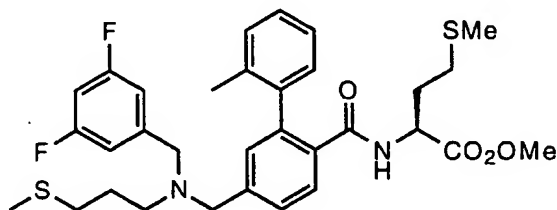


Example 1273

N-[4-N-(N-(3-methylthiopropyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

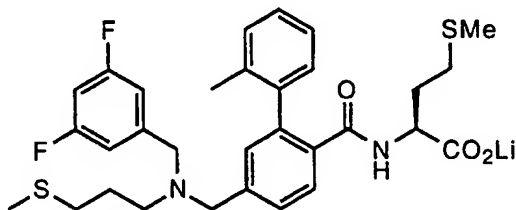
Example 1273A

Prepared according to the procedure of example 1258A from reaction between 1258A and 3-(methylthio)propionaldehyde. NMR(CDCl₃) 7.91-7.98 (m, 1H); 7.38-7.45 (m, 1H); 7.20-7.30 (m, 4H); 7.04-7.10 (m, 1H); 6.83-6.90 (m, 2H); 6.60-6.74 (m, 1H); 3.60 (s, 5H); 3.55 (s, 2H); 2.50-2.60 (t, 2H); 2.42-2.50 (t, 2H); 2.10 (s, 3H); 2.05 (s, 3H); 1.70-1.84 (m, 2H). (DSI/NH₃)/MS: 470(M+H)⁺.

Example 1273B

N-[4-N-(N-(3-methylthiopropyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

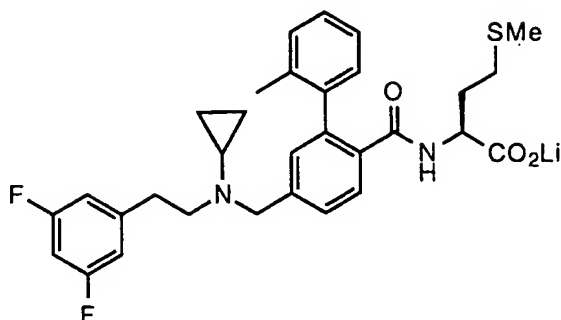
Prepared according to the procedure of example 1258C from 1273A. NMR(CDCl₃) 7.81-7.98 (m, 1H); 7.38-7.45 (m, 2H); 7.20-7.40 (m, 3H); 7.18 (s, 1H); 6.83-6.95 (m, 2H); 6.60-6.78 (m, 1H); 5.81-5.90 (m, 1H); 4.58-4.70 (m, 1H); 3.67 (s, 3H); 3.63 (s, 2H); 3.55 (s, 2H); 2.50-2.60 (t, 2H); 2.42-2.50 (t, 2H); 1.92-2.20 (m, 9H); 1.65-1.95 (m, 4H); 1.5-1.65 (m, 2H). (DSI/NH₃)/MS: 601(M+H)⁺.

Example 1273C

N-[4-N-(N-(3-methylthiopropyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

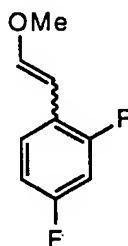
Prepared according to the procedure of example 1178J from 1273B. NMR ¹H(MeOH-d₄): 7.6-7.7 (1H, m); 7.4-7.48 (1H, m), 7.0-7.3 (6H, m); 6.9-7.0 (2H, m);

16450 6.7-6.8 (1H, m); 4.1-4.22 (1H, m); 4.65 (2H, s), 4.60 (2H, s); 2.5-2.6 (2H, m); 2.4-2.5 (2H, m); 1.8-2.3 (13H, m). ESI(-)/MS: 585(M-Li).



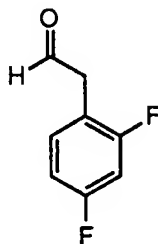
Example 1275

16455 *N*-[4-*N*-(*N*-cyclopropyl-*N*-(2-(3,5-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.



Example 1275A

16460 Prepared according to the procedure of example 1279A from the reaction between 2,4-difluorobenzaldehyde and (Methoxymethyl)triphenylphosphonium chloride. NMR. 7.18-7.21 (m, 2H); 6.80-6.94 (m, 3H); 6.06 (s, 1H); 5.84 (s, 1H); 3.78 (s, 3H). DSI/NH₃)MS: 171(M+H)⁺; 188(M+NH₄)⁺.

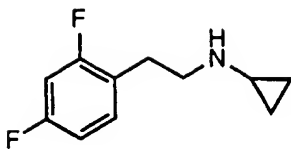


16465

Example 1275B

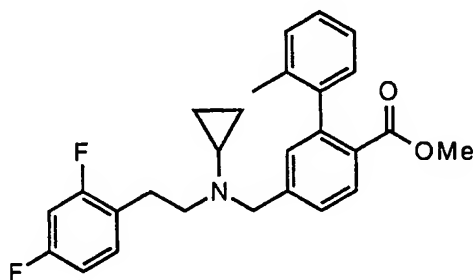
Prepared according to the procedure of example 1279B from example 1275A. NMR. 9.78 (s, 1H); 7.18-7.21 (m, 2H) 6.60-6.70 (m, 2H); ; 3.75 (s, 2H). DSI/NH₃)MS: 157(M+H)⁺; 174(M+NH₄)⁺.

16470

Example 1275C

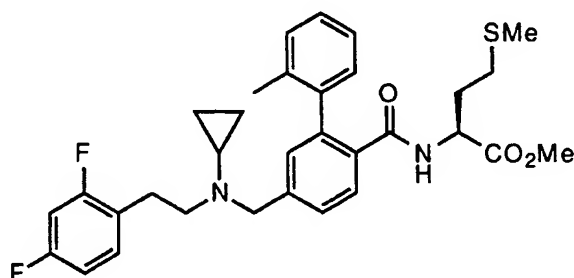
Prepared according to the procedure of example 1258A from the reaction between example 1275B and cyclopropylamine. NMR(CDCl₃) 7.18-7.21 (m, 1H); 6.74-6.82 (m, 2H); 2.80-2.90 (m, 2H); 2.80-2.90 (m, 2H); 1.80-1.98 (m, 1H); 0.40-0.60 (m, 4H); (DSI/NH₃)MS: 198(M+H)⁺.

16475

Example 1275D

Prepared according to the procedure of example of 1258A from the reaction between example 1275C and 4-formyl-2-(2-methylphenyl)benzoic acid methyl ester. NMR 7.94-8.00 (m, 1H); 7.00-7.40 (m, 7H); 6.74-6.82 (m, 2H); 3.83 (s, 2H); 3.60 (s, 3H); 2.70-2.90 (m, 4H); 2.05 (s, 3H); 1.80-2.00 (m, 1H); 0.40-0.60 (m, 4H); (DSI/NH₃)MS: 436(M+H)⁺.

16480



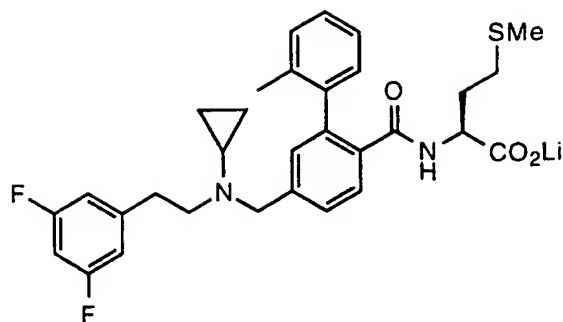
16485

Example 1275E

N-[4-N-(N-cyclopropyl-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester.

16490

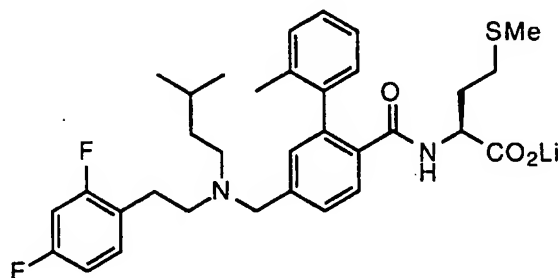
Prepared according to the procedure of example 1258C from 1275D. NMR 7.94-7.80 (m, 1H); 7.00-7.40 (m, 7H); 6.74-6.82 (m, 2H); 5.90-5.94 (m 1H); 4.60-4.70 (m, 1H); 3.83 (s, 2H); 3.75 (s, 3H); 2.80-3.00 (m, 2H); 2.00-2.00 (m, 8H); 1.80-2.00 (m, 2H); 1.50-1.70 (m, 2H); 0.40-0.60 (m, 4H); (DSI/NH₃)MS: 567(M+H)⁺.

**Example 1275F**

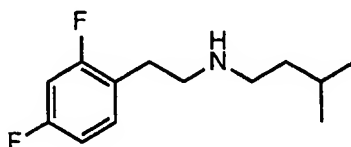
N-[4-N-(N-cyclopropyl-N-(2-(3,5-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

Prepared according to the procedure of example 1178J from 1275E. NMR

16500 ^1H (MeOH- d_4): 7.5-7.6 (1H, m); 7.25-7.35 (1H, m); 7.0-7.25 (7H, m); 6.7-6.8 (2H, m); 4.1-4.25 (1H, m); 3.8 (2H, s); 2.65-2.85 (4H, m); 1.65-2.2 (11H, m); 1.5-1.65 (1H, m); 0.4-0.5 (2H, m); 0.3-0.4 (2H, m). ESI(-)/MS: 551(M-Li). Anal. Calcd for $\text{C}_{31}\text{H}_{33}\text{N}_2\text{O}_3\text{SLi}\cdot 0.32\text{H}_2\text{O}\cdot 1.0\text{LiOH}$: C, 63.29; H, 5.93; N, 4.76. Found: C, 63.30; H, 5.77; N, 4.67.

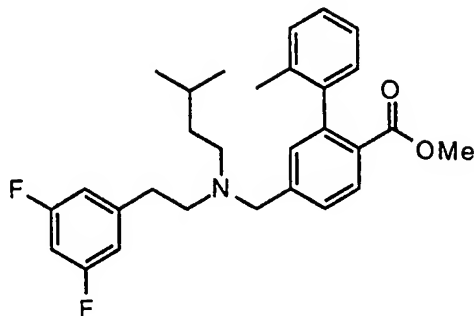
**Example 1276**

[4-N-(N-2-methylbutyl-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

**Example 1276A**

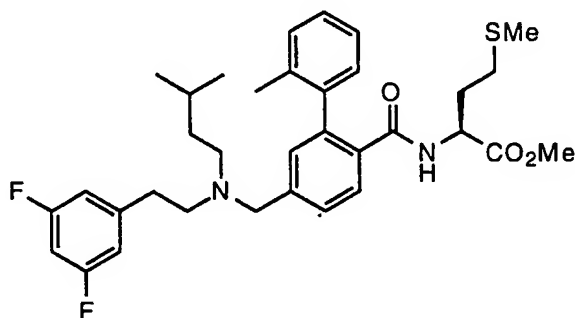
16515 Prepared according to the procedure of example 1275C from example 1275B and 3-methylbutylamine. NMR(CDCl_3) 7.14-7.22 (m, 1H); 6.74-6.82 (m, 2H); 2.78-2.90 (m,

4H); 2.60-2.68 (m, 2H); 1.50-1.70 (m, 1H); 1.30-1.50 (m, 2H); 0.9 (d, 6H).
(DSI/NH₃)MS: 228(M+H)⁺.



Example 1276B

Prepared according to the procedure of example of 1258A from the reaction between example 1276A and 4-formyl-2-(2-methylphenyl)benzoic acid methyl ester. NMR 7.94-8.00 (m, 1H); 7.00-7.40 (m, 7H); 6.74-6.82 (m, 2H); 3.83 (s, 2H); 3.60 (s, 3H); 2.60-2.90 (m, 4H); 2.50-2.60 (m, 2H); 2.05 (s, 3H); 1.40-1.60 (m, 1H); 1.24-1.48 (m, 2H); 0.90 (d, 6H). (DSI/NH₃)MS: 466(M+H)⁺.

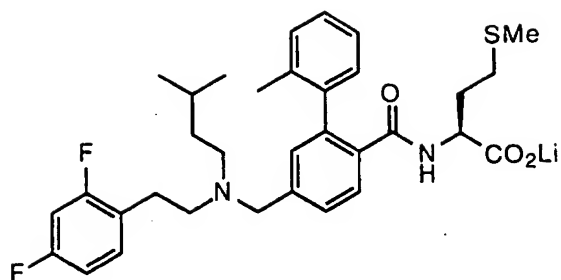


Example 1276C

[4-N-(N-2-methylbutyl-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester.

Prepared according to the procedure of example 1258C from 1276B. NMR 7.85-7.95 (m, 1H); 7.00-7.40 (m, 7H); 6.67-6.82 (m, 2H); 5.91-5.97 (m, 1H); 4.56-4.70 (m, 1H); 3.63 (s, 5H); 2.65-2.80 (m, 4H); 2.46-2.55 (m, 2H); 2.00-2.20 (m, 8H); 1.70-2.00 (m, 1H); 1.45-1.70 (m 2H); 1.30-1.40 (m, 2H); 0.90 (d, 6H). (DSI/NH₃)MS:

597(M+H)⁺.

Example 1276D

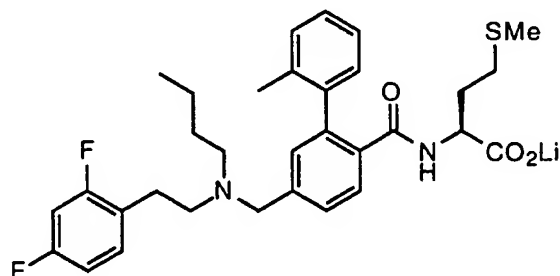
[4-N-(N-2-methylbutyl)-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt.

16540

Prepared according to the procedure of example 1178J from 1276C. NMR

^1H (MeOH- d_4): 7.5-7.6 (1H, m); 7.2-7.3 (1H, m); 7.0-7.25 (7H, m); 6.7-6.8 (2H, m); 4.1-4.25 (1H, m); 3.8 (2H, s); 2.65-2.75 (2H, m); 2.55-2.65 (2H, m); 2.4-2.5 (2H, m); 2.1 (1H, s); 1.85-2.0 (6H, m); 1.55-1.85 (2H, m); 1.5-1.65 (1H, m); 1.38-1.5 (1H, m); 1.2-1.38 (2H, m); 0.75 (6H, d). ESI(-)/MS: 581(M-Li). Anal. Calcd for $\text{C}_{33}\text{H}_{39}\text{N}_2\text{O}_3\text{SLi}\cdot 0.25\text{H}_2\text{O}\cdot 1.8\text{LiOH}$: C, 63.30; H, 5.54; N, 4.40. Found: C, 63.30; H, 6.17; N, 4.24.

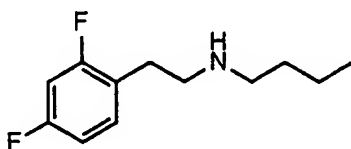
16545



16550

Example 1277

[4-N-(N-butyl)-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt.



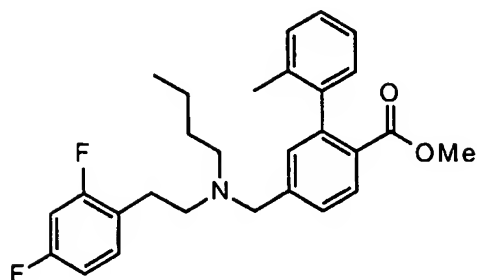
16555

Example 1277A

Prepared according to the procedure of example 1275C from example 1275B and butylamine. NMR(CDCl_3) 7.14-7.22 (m, 1H); 6.74-6.82 (m, 2H); 2.78-2.90 (m, 4H);

2.60-2.68 (m, 2H); 1.50-1.70 (m, 2H); 1.20-1.50 (m, 2H); 0.9 (d, 3H). (DSI/NH₃)MS: 214(M+H)⁺.

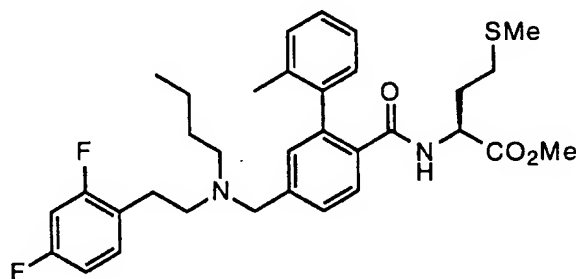
16560



Example 1277B

Prepared according to the procedure of example of 1258A from the reaction between example 1277A and 4-formyl-2-(2-methylphenyl)benzoic acid methyl ester. NMR 7.94-8.00 (m, 1H); 7.00-7.40 (m, 7H); 6.74-6.82 (m, 2H); 3.83 (s, 2H); 3.60 (s, 3H); 2.60-2.90 (m, 4H); 2.50-2.60 (m, 2H); 2.05 (s, 3H); 1.40-1.60 (m, 2H); 1.24-1.48 (m, 2H); 0.90 t, 3H). (DSI/NH₃)MS: 452(M+H)⁺.

16565



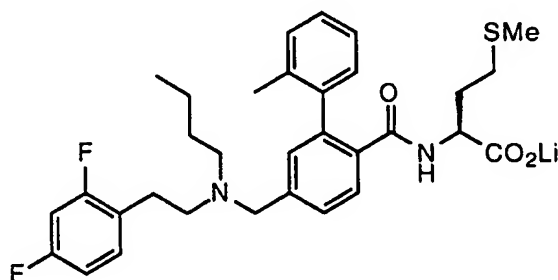
16570

Example 1277C

[4-N-(N-butyl-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester.

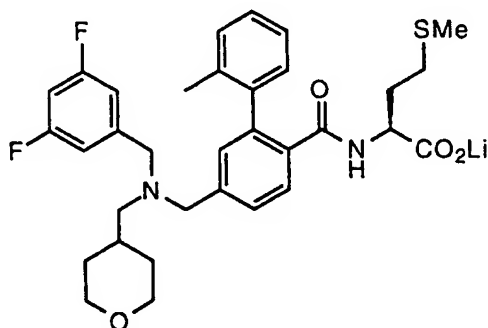
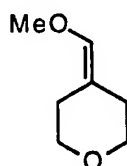
Prepared according to the procedure of example 1258C from 1277B. NMR 7.85-7.95 (m, 1H); 7.00-7.40 (m, 7H); 6.67-6.82 (m, 2H); 5.91-5.97 (m, 1H); 4.56-4.70 (m, 1H); 3.63 (s, 5H); 2.65-2.80 (m, 4H); 2.46-2.55 (m, 2H); 2.00-2.20 (m, 8H); 1.70-2.00 (m, 2H); 1.45-1.70 (m 2H); 1.30-1.40 (m, 2H); 0.90 (t, 3H). (DSI/NH₃)MS: 583(M+H)⁺.

16575



Example 1277D[4-*N*-(*N*-butyl-*N*-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

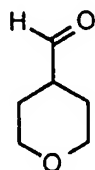
Prepared according to the procedure of example 1178J from 1277C. NMR ^1H (MeOH- d_4): 7.45-7.55 (1H, m); 7.2-7.5 (1H, m); 7.0-7.25 (7H, m); 6.65-6.75 (2H, m); 4.1-4.25 (1H, m); 3.8 (2H, s); 2.65-2.75 (2H, m); 2.55-2.65 (2H, m); 2.35-2.45 (2H, m); 2.1 (1H, s); 1.8-2.0 (6H, m); 1.65-1.85 (2H, m); 1.4-1.6 (1H, m); 1.25-1.5 (3H, m); 1.1-1.25 (2H, m); 0.75 (3H, t). ESI(-)/MS: 567(M-Li). Anal. Calcd for $\text{C}_{33}\text{H}_{39}\text{N}_2\text{O}_3\text{SLi} \cdot 1.7\text{H}_2\text{O}$: C, 63.50; H, 6.73; N, 4.63. Found: C, 63.50; H, 6.41; N, 4.29.

Example 1279*N*-[4-*N*-(*N*-(4-methyltetrahydropyran-yl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.Example 1279A

(Methoxymethyl)triphenylphosphonium chloride (25.71 g, 75 mmol) in 200 ml of anhydrous THF was treated 1.0 M sodium bis(trimethylsilyl)amide solution (75 ml, 75 mmol) at 0°C in 10 min. under N_2 . The resulted deep red solution was then stirred at 0°C for another 1 hour. To this solution, tetrahydro-4-*H*-pyran-4-one (5.0 g, 50 mmol) in 10 ml of anhydrous THF was added. After being stirred at 0°C for another 1 hour, the solution was brought up to boiling for 12 hours. The reaction mixture was concentrated under vacuum, then diluted by 1:1 ether/hexane solution, filtrated through a pack of silica gel, and washed by another 200 ml of 1:1 ether/hexane solution. The filtrate was then concentrated. Vacuum distillation of the residue afforded 3.91 g of the title compound (64%).

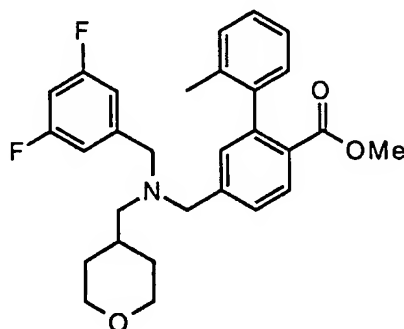
NMR(CDCl₃) 5.83 (s, 1H); 3.4-3.5 (m, 4H); 3.58 (s, 3H); 2.29-2.35 (m, 2H); 2.05-2.15 (m, 2H). DSI/NH₃/MS: 129(M+H)⁺; 146(M+NH₄)⁺.

16610

Example 1279B

1279A (0.9 g, 7 mmol) in 15 ml of 88% formic acid plus 5 ml of water was refluxed for 3 hours under N₂. After the solvents were removed by rotavapor, the residue was purified by flash chromatography eluting 3:7 EtOAc/hexane to afford 0.60 g of title compound (75%). NMR(CDCl₃) 9.62 (s, 1H); 3.85-3.92 (m, 2H); 3.30-3.40 (m, 2H); 1.60-1.85 (m, 3H); 1.05-1.20 (m, 2H). DSI/NH₃/MS: 115(M+H)⁺; 132(M+NH₄)⁺.

16615

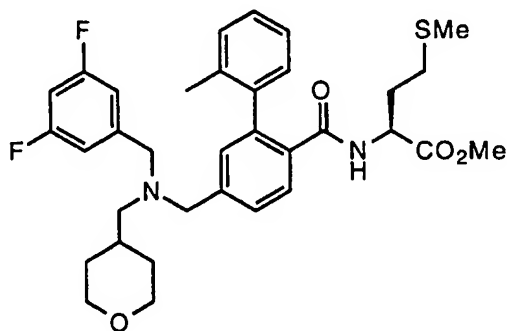


16620

Example 1279C

Prepared according to the procedure of example 1258A from reaction between 1258A and 1279B. NMR(CDCl₃) 7.92-7.99 (m, 1H); 7.35-7.45 (m, 1H); 7.20-7.30 (m, 4H); 7.05-7.10 (m, 1H); 6.82-6.90 (m, 2H); 6.62-6.73 (m, 1H); 3.88-3.98 (m, 2H); 3.61 (s, 3H); 3.59 (s, 2H); 3.52 (s, 2H); 3.25-3.40 (m, 2H); 2.25-2.31 (m, 2H); 2.05 (s, 3H); 1.60-1.90 (m, 3H); 1.00-1.20 (m, 2H). DSI/NH₃/MS: 480(M+H)⁺.

16625

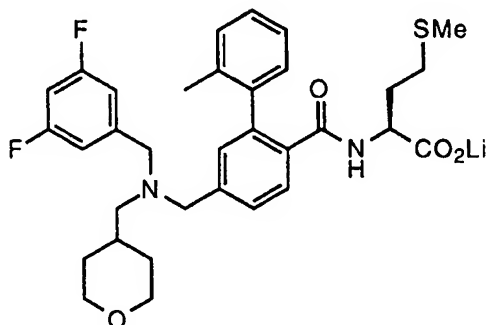
Example 1279D

N-[4-*N*-(*N*-(4-methyltetrahydropyran-yl))-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

16630

Prepared according to the procedure of example 1258C from 1279C. NMR(CDCl₃) 7.88-7.99 (m, 1H); 7.35-7.45 (m, 1H); 7.18-7.30 (m, 5H); 6.80-6.90 (m, 2H); 6.62-6.73 (m, 1H); 5.85-5.92 (m, 1H); 4.52-4.70 (m, 1H); 3.88-3.98 (m, 2H); 3.61 (s, 3H); 3.60 (s, 2H); 3.50 (s, 2H); 3.30-3.40 (m, 2H); 2.20-2.31 (m, 2H); 2.0-2.2 (m, 9H); 1.78-1.98 (m, 2H); 1.55-1.78 (m, 3H); 1.00-1.20 (m, 2H). DSI/NH₃/MS: 611(M+H)⁺.

16635



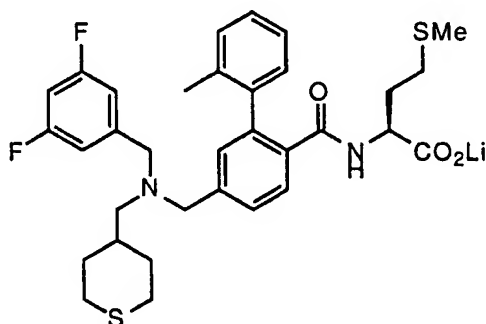
Example 1279E

N-[4-*N*-(*N*-(4-methyltetrahydropyran-yl))-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

16640

Prepared according to the procedure of example 1178J from 1279D. NMR ¹H(MeOH-d₄): 7.6-7.7 (1H, m); 7.38-7.48 (1H, m), 7.0-7.28 (6H, m); 6.9-7.0 (2H, m); 6.78-6.88 (1H, m); 4.1-4.22 (1H, m); 3.8-3.9 (2H, m); 3.8 (2H, s); 3.75 (2H, s); 3.4 (2H, m); 2.3-2.38 (2H, m); 2.25 (1H, s); 1.76-2.1 (14H, m); 1.0-1.2 (2H, m). ESI(-)/MS: 595(M-Li). Anal. Calcd for C₃₃H₃₇F₂N₂O₄SLi•0.52H₂O: C, 64.76; H, 6.26; N, 4.58. Found: C, 64.76; H, 6.01; N, 4.45.

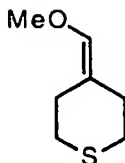
16645



16650

Example 1280

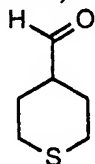
N-[4-*N*-(*N*-(4-methyltetrahydrothiopyran-yl))-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.



16655

Example 1280A

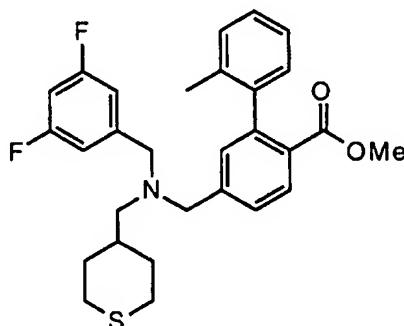
Prepared according to the procedure of example 1279A from tetrahydrothiopyran-4-one. NMR(CDCl₃) 5.82 (s, 3H); 3.58 (s, 3H); 2.38-2.43 (m, 4H); 2.30-2.38 (m, 2H); 2.05-2.12 (m, 2H). DSI/NH₃/MS: 145(M+H)⁺.



16660

Example 1280B

Prepared according to the procedure of example 1279B from 1280A. NMR(CDCl₃) 9.65 (s, 1H); 2.60-2.80 (m, 4H); 2.20-2.40 (m, 2H); 1.70 1.88 (m, 2H). DSI/NH₃/MS: 131(M+H)⁺.

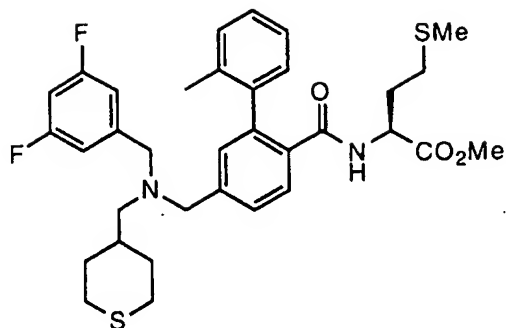


16665

Example 1280C

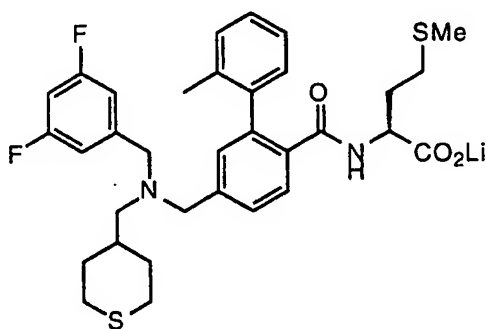
Prepared according to the procedure of example 1258A from reaction between 1258A and 1280B. NMR(CDCl₃) 8.00-8.08 (m, 1H); 7.40-7.46 (m, 1H); 7.10-7.30 (m, 4H); 7.05-7.10 (m, 1H); 6.80-6.90 (m, 2H); 6.85-6.73 (m, 1H); 3.60 (s, 5H); 3.50 (s, 2H); 2.50-2.70 (m, 4H); 2.20-2.30 (m, 2H); 2.00-2.20 (m, 5H); 1.40-1.70 (m, 3H); 1.12-1.30 (m, 2H). DSI/NH₃/MS: 496(M+H)⁺.

16670

Example 1280D

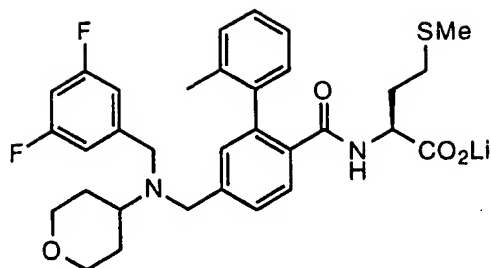
16675 *N*-[4-*N*-(*N*-(4-methyltetrahydrothiopyran-yl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester.

Prepared according to the procedure of example 1258C from 1280C. NMR(CDCl₃) 7.85-8.00 (m, 1H); 7.1-7.45 (m, 6H); 6.80-6.90 (m, 2H); 6.65-6.76 (m, 1H); 5.84-5.94 (m, 1H); 4.55-4.70 (m, 1H); 3.65 (s, 3H); 3.52 (s, 2H); 3.45 (s, 2H); 2.50-2.70 (m, 4H); 2.00-2.30 (m, 13H); 1.78-2.00 (m, 1H); 1.50-1.65 (m, 2H); 1.05-1.30 (m, 2H). DSI/NH₃/MS: 626(M+H)⁺.

Example 1280E

16685 *N*-[4-*N*-(*N*-(4-methyltetrahydrothiopyran-yl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

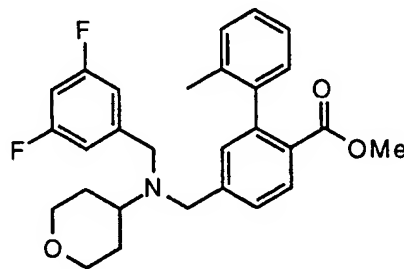
Prepared according to the procedure of example 1178J from example 1280D. NMR ¹H(MeOH-d₄): 7.6-7.7 (1H, m); 7.38-7.48 (1H, m), 7.0-7.35 (6H, m); 6.9-7.0 (2H, m); 6.75-6.85 (1H, m); 4.1-4.22 (1H, m); 3.6 (2H, s); 3.55(2H, s); 3.35 (2H, s); 2.4-2.65 (4H, m); 2.2-2.3 (3H, m); 1.78-2.1 (8H, m); 1.6-1.78 (2H, m); 1.05-1.2 (2H, m). ESI(-)/MS: 593(M-Li). Anal. Calcd for C₃₃H₃₇F₂N₂O₄S₂Li•1.21H₂O•1.0LiOH: C, 59.65; H, 6.13; N, 4.22. Found: C, 59.65; H, 5.85; N, 3.89.



16695

Example 1281

N-[4-N-(N-(4-tetrahydropyran-yl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

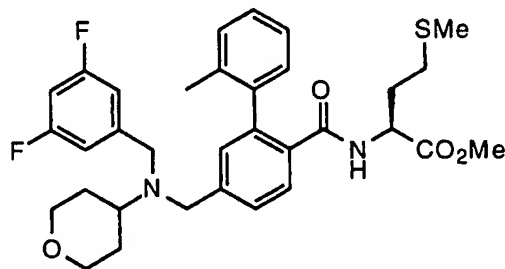


16700

Example 1281A

Prepared according to the procedure of example 1258A from reaction between 1258A and tetrahydro-4-*H*-pyran-4-one. NMR(CDCl₃) 7.80-7.95 (m, 1H); 7.35-7.45 (m, 1H); 7.15-7.30 (m, 4H); 7.04-7.10 (m, 1H); 6.80-6.89 (m, 2H); 6.58-6.70 (m, 1H); 3.95-4.03 (m, 2H); 3.70 (s, 2H); 3.65 (s, 2H); 3.60 (s, 3H); 3.20-3.35 (m, 2H); 2.65-2.80 (m, 1H); 2.05 (s, 3H); 1.60-1.80 (m, 4H). (ESI/NH₃)/MS: 466(M+H)⁺.

16705

Example 1281B

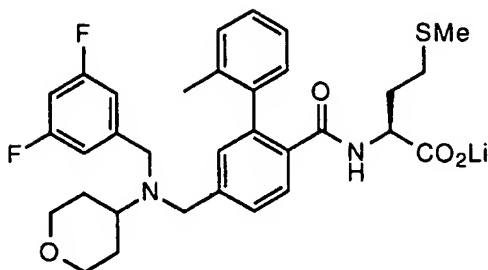
16710

N-[4-N-(N-(4-tetrahydropyran-yl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Prepared according to the procedure of example 1258C from 1281A. NMR(CDCl₃) 7.81-7.98 (m, 1H); 7.38-7.45 (m, 1H); 7.20-7.40 (m, 4H); 7.18 (s, 1H); 6.83-6.91 (m, 2H); 6.60-6.70 (m, 1H); 5.81-5.90 (m, 1H); 4.58-4.70 (m, 1H); 3.95-4.02 (m, 2H); 3.70 (s, 2H); 3.63 (s, 2H); 3.60 (s, 2H); 3.20-3.38 (m, 1H); 2.55-2.80 (m, 1H); 1.92-2.20 (m,

16715

8H); 1.75-1.95 (m, 1H); 1.61-1.78 (m, 3H). 1.50-1.65 (m, 2H); (ESI/NH₃)/MS: 597(M+H)⁺.



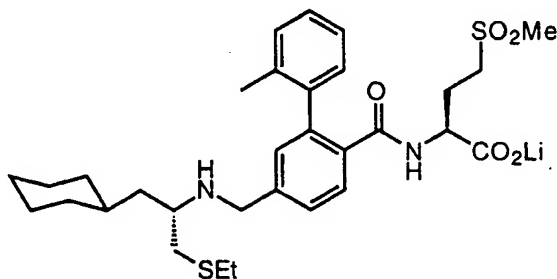
16720

Example 1281C

N-[4-N-(N-(4-tetrahydropyran-yl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt.

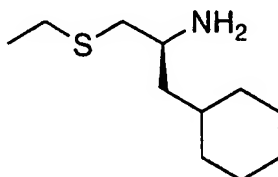
Prepared according to the procedure of example 1178J from 1281B. NMR ¹H(MeOH-d₄): 7.58-7.68 (1H, m); 7.38-7.48 (1H, m), 7.0-7.28 (6H, m); 6.9-7.0 (2H, m); 6.78-6.88 (1H, m); 4.1-4.22 (1H, m); 3.9-4.0 (2H, m); 3.75 (2H, s); 3.7 (2H, s); 3.3 (2H, m); 2.7-2.85 (1H, m); 2.2 (1H, s); 1.76-2.1 (14H, m). ESI(-)/MS: 586(M-Li). Anal. Calcd for C₃₂H₃₅F₂N₂O₄SLi•2.07H₂O: C, 61.41; H, 6.30; N, 4.37. Found: C, 61.40; H, 6.05; N, 4.37.

16730

Example 1313

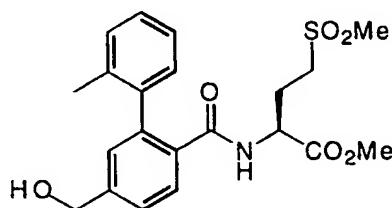
N-[4-N-(3-Cyclohexyl-1-ethylthioprop-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate Lithium Salt

16735

Example 1313A

2-Amino-3-cyclohexyl-1-ethylthioprop-2-ylamine

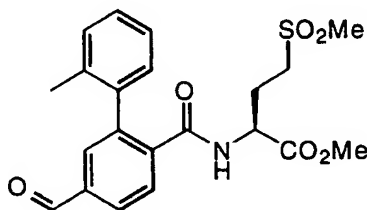
Trifluoroacetic acid (3 mL) was added to a solution of the product from Example 403C (274 mg, 0.9 mmol) in CH₂Cl₂ (3 mL) at ambient temperature. After 30 min of stirring, solvent was removed and the residue redissolved in CH₂Cl₂, washed with a solution of saturated K₂CO₃, dried (MgSO₄) and concentrated. The crude product was chromatographed (silica gel; CHCl₃/MeOH, 90:10) to afford a clear oil (162 mg, 75%): ¹H NMR (CDCl₃, 300 MHz) δ 2.97 (m, 1H), 2.68 (dd, J=13, 4 Hz, 1H), 2.55 (q, J=7.5 Hz, 2H), 2.34 (dd, J=13, 8.5 Hz, 1H), 1.80-1.61 (m, 5H), 1.50-1.10 (m, 6H), 1.26 (t, J=7.5 Hz, 3H), 1.00-0.90 (m, 2H); MS (CI/NH₃) m/z: 202 (M+H)⁺.



Example 1313B

Methyl-N-[4-hydroxymethyl-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfonylbutanoate

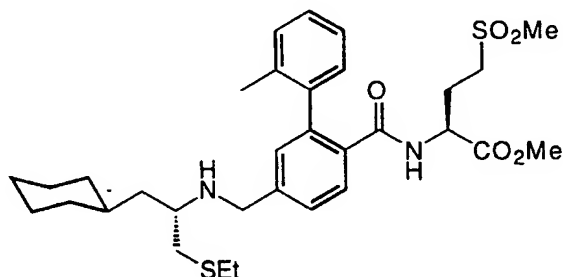
The product from Example 1178C (1.0 g, 4.1 mmol) in MeOH (12 mL) was combined with a solution of saturated LiOH (4.0 mL) and heated at reflux for 3.5 hours. The mixture was allowed to cool to ambient temperature and then extracted with Et₂O. The phases were separated and concentrated HCl added to the aqueous phase which was extracted with EtOAc (2X). The EtOAc phases were combined, dried (MgSO₄) and concentrated to dryness to afford the crude acid as a white solid. MS (CI/NH₃) m/z: 243 (M+H)⁺. The crude acid, EDCI (940 mg, 4.5 mmol), Hobt (1.1 g, 8.2 mmol), (L)-methionine sulfone methyl ester hydrochloride (1.0 mg, 4.5 mmol) and DIEA (2.1 mL, 12.3 mmol) in DMF (15 mL) were allowed to react in a manner similar to that described in Example 608 D. The crude residue was chromatographed (silica gel; MeOH/CHCl₃, 5:95) to afford the title compound (963 mg, 56%).



Example 1313C

Methyl-N-[4-formyl-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfonylbutanoate

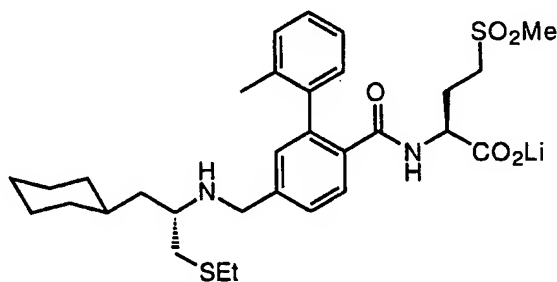
Dimethylsulfoxide (325 μ L, 4.6 mmol) was added to a solution of oxalyl chloride (200 μ L, 2.5 mmol) at -78°C . After stirring for 5 min, the product from Example 1313B (955 mg, 2.3 mmol) in CH_2Cl_2 (2.5 mL) was added to the reaction vessel. After 15 min, TEA (950 μ L, 6.8 mL) was added to the reaction mixture and the cold bath was removed. After stirring for 30 min, a solution of 2N HCl was added to the mixture and the phases separated. The organic phase was dried (MgSO_4) and concentrated. The residue was chromatographed (silica gel; $\text{MeOH}/\text{CHCl}_3$, 2:98) to afford a clear oil (866 mg, 91%). ^1H NMR (CDCl_3 , 300 MHz) δ 1.88 (m, 1H), 2.11-2.30 (m, 4H), 2.47-2.73 (m, 2H), 2.71 (s, 3H), 3.71 (s, 3H), 4.65 (m, 1H), 6.12 (dd, $J=8.8$ Hz, 1H), 7.20 (d, $J=7$ Hz, 1H), 7.27-7.41 (m, 2H), 7.76 (s, 1H), 7.95-8.06 (m, 2H), 10.10 (s, 1H); MS (CI/NH_3) m/z : 418 ($\text{M}+\text{H}$) $^+$.



Example 1313D

Methyl-N-[4-(N-(3-Cyclohexyl-1-ethylthioprop-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate

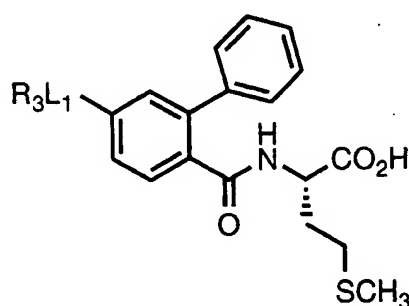
The product from Example 1313A (285 mg, 1.4 mmol), the product from Example 1313C (618 mg, 1.5 mmol) and sodium triacetoxyborohydride (415 mg, 2.0 mmol) were combined in 1,2-dichloroethane (6 mL) at ambient temperature and allowed to stir for 18 hours. A solution of saturated NaHCO_3 was added and the mixture was extracted with EtOAc (2X). The EtOAc phases were combined, dried (MgSO_4) and concentrated. The residue was chromatographed (silica gel; $\text{MeOH}/\text{CHCl}_3$, 2:98) to afford a clear oil (753 mg, 89%). MS (CI/NH_3) m/z : 418 ($\text{M}+\text{H}$) $^+$.



Example 1313E

N-[4-(*N*-(3-Cyclohexyl-1-ethylthioprop-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate Lithium Salt

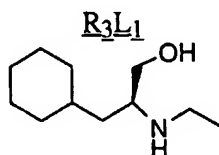
16795 The product from Example 1313D (748 mg, 1.2 mmol) was allowed to react with lithium hydroxide monohydrate (55 mg, 1.3 mmol) in a manner similar to that described in Example 608E to afford the title compound. ¹H NMR (DMSO-d₆, 300 MHz) δ 0.70-0.91 (m, 2H), 1.12-1.65 (m, 14H), 1.75-2.20 (m, 5H), 2.35-2.67 (m, 7H), 2.82 (s, 3H), 3.66-3.86 (m, 3H), 6.95 (m, 1H), 7.10-7.25 (m, 4H), 7.38 (d, J=8 Hz, 1H), 7.53 (d, J=8 Hz, 1H); MS (APCI(-)) m/z: (M-H)⁻ 587; Anal. Calcd for C₃₁H₄₃LiN₂O₅S₂•1.90 H₂O: C, 59.20; H, 7.50; N, 4.45. Found: C, 59.22; H, 7.16; N, 4.36.



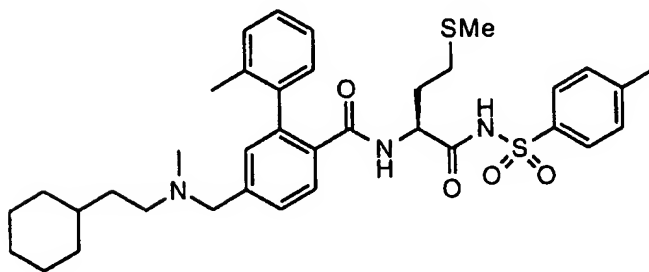
16805

Example 1317

Example
1317



MS (M+H)[±]
499



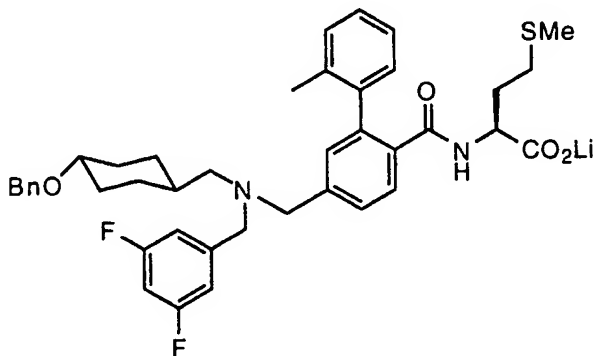
16810

Example 1319

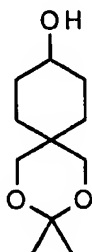
N-[4-(*N*-Methyl-*N*-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine p-tolylsulfonimide

The above compound was prepared from the compound described in Example 608E and p-toluenesulfonamide by the method of Example 1216A, except the reaction was

16815 worked up by diluting with CHCl_3 (instead of EtOAc), there was no HCl wash, and the chromatography was done with EtOAc/water/ $\text{CH}_3\text{CO}_2\text{H}$ 19/0.5/0.5, then 18/1/1. ^1H NMR (CDCl_3) δ 7.80 (m, 3H), 7.58 (dd, 1H), 7.22 (m, 7H), 6.18 (m, 1H), 4.20 (m, 1H), 3.98 (s, 2H), 2.80 (m, 2H), 2.55 (s, 3H), 2.40 (s, 3H), 2.00 (m, 8H), 1.60 (m, 8H), 1.40, 1.20. 0.90 (all m, total 7H). MS (ESI) 648 ($\text{M}-\text{H}$) $^-$. Anal calcd for $\text{C}_{36}\text{H}_{47}\text{N}_3\text{O}_4\text{S}_2 \cdot 1.00$ 16820 H_2O : C, 64.74; H, 7.39; N, 6.29. Found: C, 64.53; H, 7.22; N, 6.06.

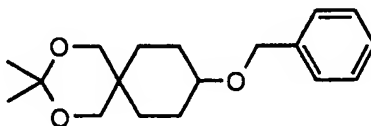
Example 1332

16825 *N*-[4-*N*-(*N*-(*trans*-4-hydroxycyclohexyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

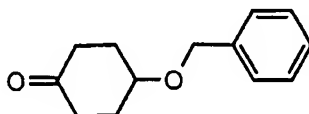
Example 1332A

16830 A mixture of 1,4-cyclohexanedione *mono*-2,2-dimethyltrimethylene ketal (1.98 g, 10 mmol), and sodium borohydride (0.757 g, 20 mmol) in 100 ml of methanol was stirred for 12 hours. The methanol was removed under reduced pressure. The residue was taken into ethyl acetate, washed by 10 % NaOH and brine respectively, and the dried over anhydrous MSG. Yield: 1.60 g (80%). (SDI/ NH_3) MS: 201($\text{M}+\text{H}$) $^+$; 218($\text{M}+\text{NH}_4$) $^+$.

16835

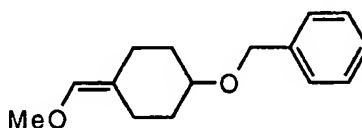
Example 1332B

Prepared according to the procedure of example 1252 from the reaction between example 1332A and benzyl bromide. NMR(CDCl₃) 7.20-7.35 (m, 5H); 4.57 (s, 2H); 3.45-3.55 (m, 6H); 2.00-2.15 (m, 2H); 1.50-1.82 (m, 5H). (SDI/NH₃) MS: 291(M+H)⁺; 308(M+NH₄)⁺.



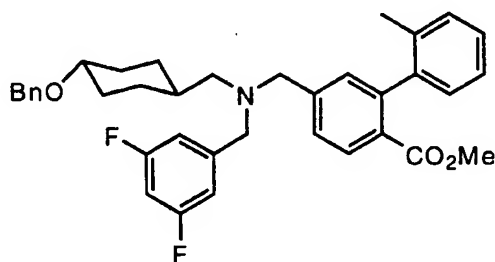
Example 1332C

Prepared according to the procedure of example of example 1266A from the reaction of example 1232B and HCl. NMR(CDCl₃) 7.23-7.40 (m, 5H); 4.60 (s, 2H); 3.78-4.08 (m, 1H); 2.55-2.70 (m, 2H); 2.20-2.35 (m, 2H); 2.10-2.20 (m, 2H); 1.90-2.01 (m, 2H). (SDI/NH₃) MS: 222(M+H)⁺; 239(M+NH₄)⁺.



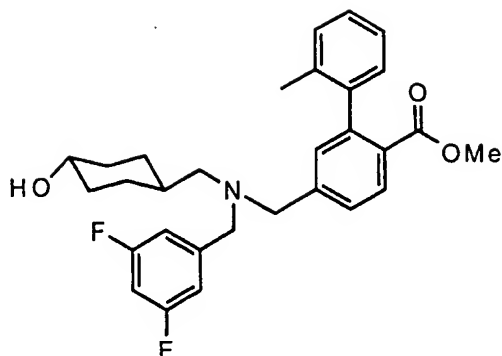
Example 1332D

Prepared according to the procedure of example 1279A from the reaction between example 1232C and (Methoxymethyl)triphenylphosphonium chloride. NMR(CDCl₃) 7.23-7.40 (m, 5H); 5.85 (s, 1H); 4.60 (s, 2H); 3.63-3.75 (m, 5H); 2.58-2.70 (m, 1H); 2.10-2.30 (m, 1H); 1.4-2.0 (m, 5H). (SDI/NH₃) MS: 233(M+H)⁺; 250(M+NH₄)⁺.



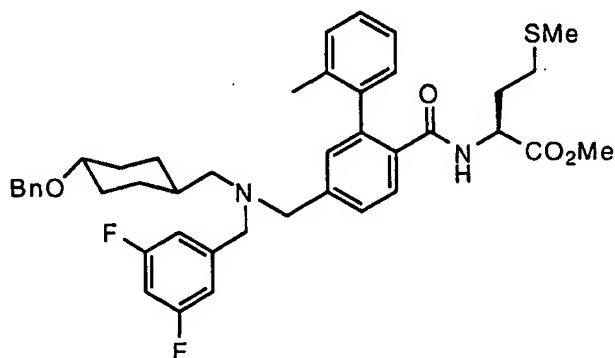
Example 1332E

Example 1332D was hydrolyzed in formic acid according to the example 1279B to give corresponding aldehyde, which was used to react with example 1258A to give two isomers. One is example 1232E, the other is example 1233A. NMR(CDCl₃) 7.90-7.95 (m, 1H); 7.38-7.44 (m, 1H); 7.13-7.39 (m, 9H); 7.02-7.10 (m, 1H); 6.83-6.92 (m, 2H); 6.60-6.70 (m, 1H); 4.55 (s, 2H); 3.60 (s, 3H); 3.55 (m, 2H); 3.50 (m, 2H); 3.18-4.30 (m, 1H); 2.18-2.21 (m, 2H); 2.0-2.18 (m, 4H); 1.80-2.00 (m, 2H); 1.40-1.60 (m, 2H); 1.09-1.32 (m, 2H); 0.67-0.83 (m, 2H). (SDI/NH₃) MS: 584(M+H)⁺.

**Example 1332F**

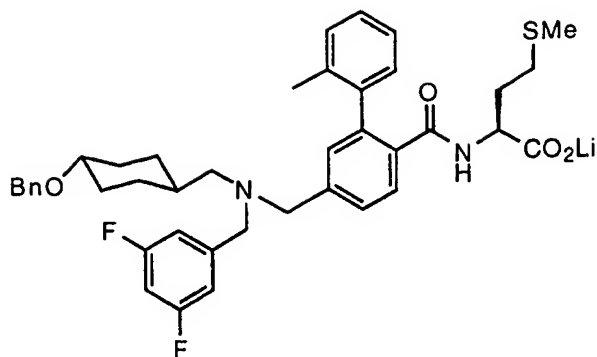
A mixture of 1332D (0.07 g, 0.12 mmol) and 0.1 ml of trimethylsilyl iodide in 2 ml of methylene chloride was stirred until TLC indicated that there was no starting material left. Flash chromatography of the residue afforded 0.042 g of the title compound (71%).

NMR(CDCl₃) 7.90-7.95 (m, 1H); 7.40-7.44 (m, 1H); 7.13-7.39 (m, 4H); 7.02-7.10 (m, 1H); 6.83-6.92 (m, 2H); 6.60-6.70 (m, 1H); 3.60 (s, 3H); 3.55 (m, 2H); 3.50 (m, 2H); 3.18-4.30 (m, 1H); 2.18-2.21 (m, 2H); 2.0-2.18 (m, 4H); 1.80-2.00 (m, 2H); 1.40-1.60 (m, 2H); 1.09-1.32 (m, 2H); 0.67-0.83 (m, 2H). (SDI/NH₃) MS: 494(M+H)⁺.

**Example 1332G**

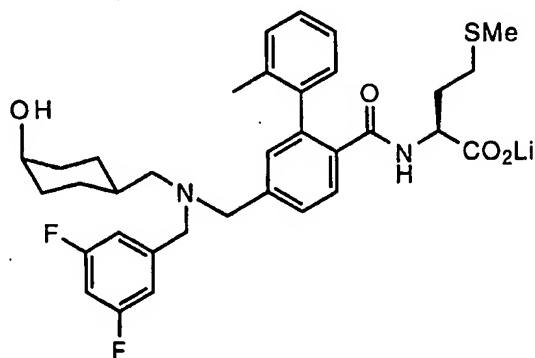
Prepared according to the procedure of example 1258C from example 1232F.

NMR(CDCl₃) 7.83-7.95 (m, 1H); 7.40-7.44 (m, 1H); 7.13-7.40 (m, 4H); 7.02-7.10 (m, 1H); 6.83-6.92 (m, 2H); 6.60-6.70 (m, 1H); 5.84-5.90 (m, 1H); 4.55-4.67 (m, 1H); 3.60 (s, 3H); 3.55 (m, 2H); 3.50 (m, 2H); 3.18-4.30 (m, 1H); 2.18-2.21 (m, 2H); 1.80-2.25 (m, 16H); 1.40-1.60 (m, 2H); 1.09-1.32 (m, 2H); 0.67-0.83 (m, 2H). (SDI/NH₃) MS: 624(M+H)⁺.

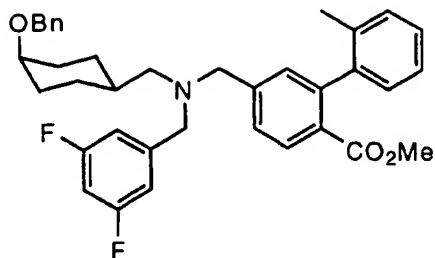
**Example 1332H**

N-[4-*N*-(*N*-(*trans*-4-hydroxycyclohexyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

16890 Prepared according to the procedure of example 1178J from example 1332G.
 NMR(CDCl₃) 7.60-7.70 (m, 1H); 7.40-7.44 (m, 1H); 7.13-7.40 (m, 5H); 6.83-7.00 (m, 2H); 6.68-6.72 (m, 1H); 4.20-4.30 (m, 1H); 3.60 (m, 2H); 3.55 (m, 2H); 3.18-4.30 (m, 1H); 2.18-2.21 (m, 2H); 1.80-2.25 (m, 16H); 1.40-1.60 (m, 2H); 1.09-1.32 (m, 2H); 0.67-0.83 (m, 2H). ESI(-)/MS: 609(M-Li). Anal. Calcd for C₃₄H₃₉F₂N₂O₄SLi•2.00
 16895 LiOH: C, 61.45; H, 6.22; N, 4.22. Found: C, 61.56; H, 5.88; N, 3.94.

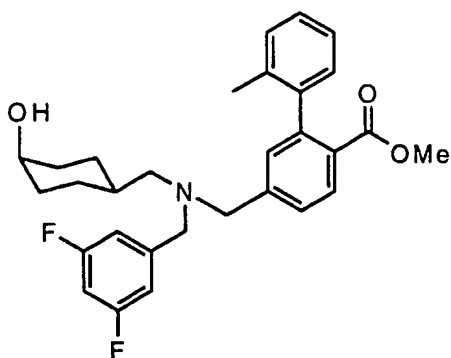
**Example 1333**

16900 *N*-[4-*N*-(*N*-(*cis*-4-hydroxycyclohexyl)-*N*-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

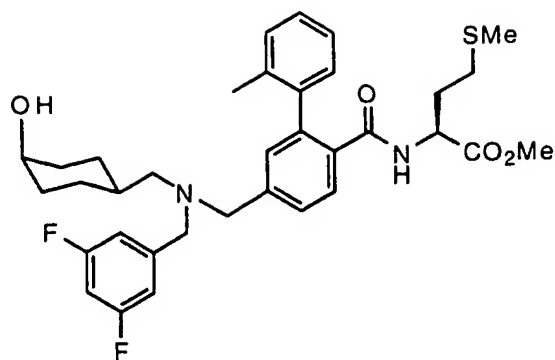
Example 1333A

16905 Prepared according to the procedure of example 1332E. NMR(CDCl₃) 7.90-7.95 (m, 1H); 7.38-7.44 (m, 1H); 7.13-7.39 (m, 9H); 7.02-7.10 (m, 1H); 6.83-6.92 (m, 2H); 6.60-6.70 (m, 1H); 4.55 (s, 2H); 3.90-4.00 (m, 1H); 3.60 (s, 3H); 3.55 (m, 2H); 3.50 (m, 2H); 3.18-4.30 (m, 1H); 2.18-2.21 (m, 2H); 2.0-2.18 (m, 3H); 1.80-2.00 (m, 2H); 1.40-1.60 (m, 2H); 1.09-1.32 (m, 2H); 0.67-0.83 (m, 2H). (SDI/NH₃) MS: 584(M+H)⁺.

16910

Example 1333B

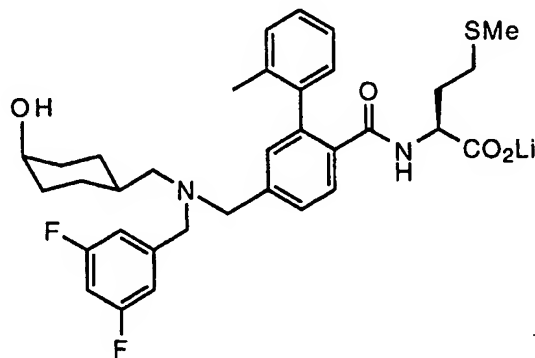
16915 Prepared according to the procedure of example 1332F from the reaction between 1333B and trimethylsilyl iodide. NMR(CDCl₃) 7.90-7.95 (m, 1H); 7.40-7.44 (m, 1H); 7.13-7.39 (m, 4H); 7.02-7.10 (m, 1H); 6.83-6.92 (m, 2H); 6.60-6.70 (m, 1H); 3.90-4.00 (m, 1H); 3.60 (s, 3H); 3.55 (m, 2H); 3.50 (m, 2H); 3.18-4.30 (m, 1H); 2.18-2.21 (m, 2H); 2.0-2.18 (m, 3H); 1.80-2.00 (m, 2H); 1.40-1.60 (m, 2H); 1.09-1.32 (m, 2H); 0.67-0.83 (m, 2H). (SDI/NH₃) MS: 494(M+H)⁺.



Example 1333C

Prepared according to the procedure of example 1258C from example 1333B.

NMR(CDCl₃) 7.83-7.95 (m, 1H); 7.40-7.44 (m, 1H); 7.13-7.40 (m, 4H); 7.02-7.10 (m, 1H); 6.83-6.92 (m, 2H); 6.60-6.70 (m, 1H); 5.84-5.90 (m, 1H); 4.55-4.67 (m, 1H); 3.92-4.02 (m, 1H); 3.60 (s, 3H); 3.55 (m, 2H); 3.50 (m, 2H); 3.18-4.30 (m, 1H); 2.18-2.21 (m, 2H); 1.80-2.25 (m, 15H); 1.40-1.60 (m, 2H); 1.09-1.32 (m, 2H); 0.67-0.83 (m, 2H). (SDI/NH₃) MS: 624(M+H)⁺.

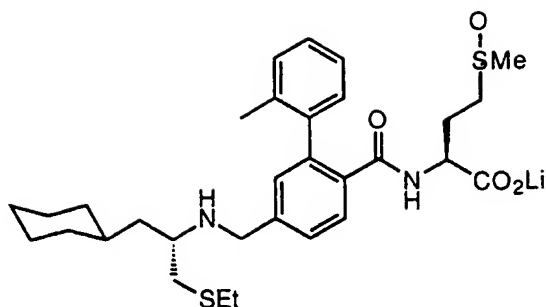


Example 1333D

N-[4-N-(N-(cis-4-hydroxycyclohexyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

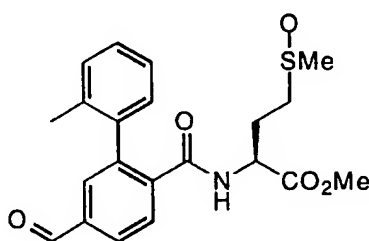
Prepared according to the procedure of example 1178J from example 1333C.

NMR(CDCl₃) 7.60-7.70 (m, 1H); 7.40-7.44 (m, 1H); 7.13-7.40 (m, 5H); 6.83-7.00 (m, 2H); 6.68-6.72 (m, 1H); 4.20-4.30 (m, 1H); 3.92-4.01 (m, 1H); 3.60 (m, 2H); 3.55 (m, 2H); 3.18-4.30 (m, 1H); 2.18-2.21 (m, 2H); 1.80-2.25 (m, 15H); 1.40-1.60 (m, 2H); 1.09-1.32 (m, 2H); 0.67-0.83 (m, 2H). ESI(-)/MS: 609(M-Li). Anal. Calcd for C₃₄H₃₉F₂N₂O₄SLi•2.50 LiOH•0.57H₂O: C, 62.58; H, 6.26; N, 4.29. Found: C, 61.61; H, 5.99 N, 3.92.

Example 1334

(2S) 2-N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate Lithium Salt

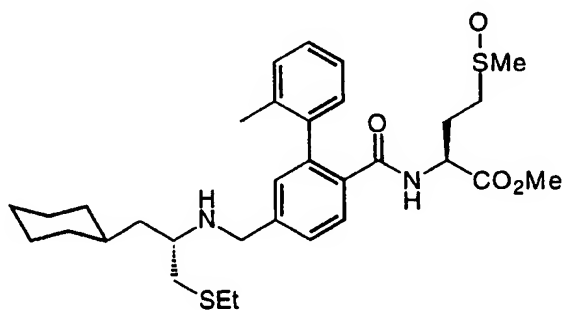
16945

Example 1334A

(2S) 2-N-[4-formyl-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, Methyl Ester

16950

The title compound was prepared from N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester (example 403G) according to the procedure in example 1071D, and was isolated as a light yellow oil. MS(APCI(+)) 402 (M+H)⁺. MS(APCI(-)) 436 (M+Cl)⁻, 400 (M-H)⁻.

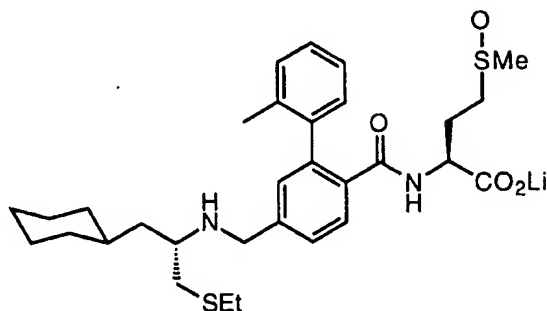
Example 1334B

(2S) 2-N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, Methyl Ester

The title compound was prepared according to example 403H, substituting (2S) 2-N-[4-formyl-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate methyl ester for N-

16960

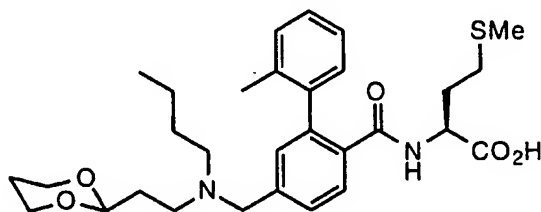
[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester. MS(APCI(+)) 587 (M+H)⁺. MS(APCI(-)) 621 (M+Cl)⁻.



Example 1334C

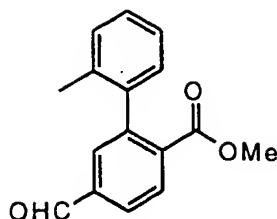
(2S) 2-N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, Lithium Salt

The title compound was prepared from (2S) 2-N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate methyl ester according to the procedure in example 608E, with the exception that the product was isolated as a light yellow foam after concentrating a methanolic solution under reduced pressure. ¹H NMR (300 MHz, DMSO) δ 0.66-0.90 (m, 2H), 1.02-1.80 (m, 13H), 1.10 (t, J=7.2 Hz, 3H), 1.96-2.21 (m, 5H), 2.36 (s, 1.5H), 2.39 (s, 1.5H), 2.41 (q, J=7.2 Hz, 2H), 2.56-2.67 (m, 3H), 3.60-3.84 (m, 4H), 6.98 (brd, J=6 Hz, 1H), 7.08-7.23 (m, 5H), 7.38 (d, J=8.4 Hz, 1H), 7.49 (d, J=7.8 Hz, 0.5H), 7.51 (d, J=7.8 Hz, 0.5H). MS (APCI(-)) m/e 571 (M-H).



Example 1335

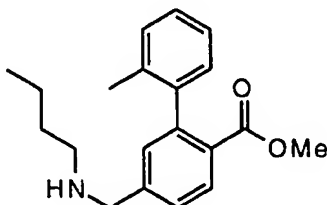
N-[4-(N-(2-(1,3-dioxan-2-ylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine



Example 1335A

4-Formyl-2-(2-methylphenyl)benzoic acid methyl ester

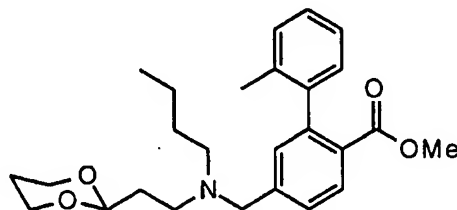
Following the procedure of example 1134D, example 1178 C (3.30 g, 11.82 mmol) provided 3.00 g 100% of the title compound. MS (DCI, NH₃): 255 (MH⁺).



Example 1335B

4-n-Butylaminomethyl-2-(2-methylphenyl)benzoic acid methyl ester

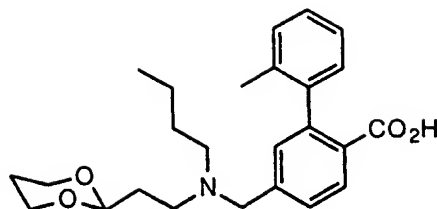
Following the procedure of example 1106D, part 1 example 1335A (1.27 g, 5.00 mmol) and butyl amine (0.99 mL, 10.00 mmol) provided 1.45 g (94%) of the title compound. MS (DCI, NH₃): 312 (MH⁺).



Example 1335C

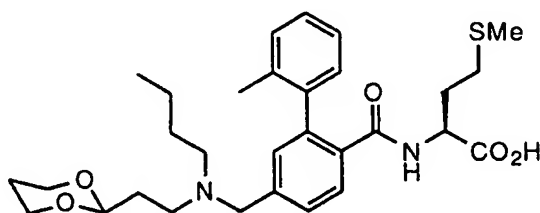
4-(N-(2-(1,3-dioxan-2-ylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester

A solution of example 1335B (359 mg 1.15 mmol), 2-bromoethyl-1,3-dioxane (164 μ L, 1.2 mmol), TBAI (443 mg, 1.2 mmol) and diisopropylethylamine (260 μ L, 1.5 mmol) in 3 mL of DMF were heated to 60°C for 72 hours. The cooled reaction mixture was diluted with water and extracted with 3 portions of ethyl ether. The combined organic extracts were washed with water, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (25 g, 25% ethyl acetate/hexanes) provided 330 mg (78%) of the title compound. MS: (ESI⁺) 426 (MH⁺).

Example 1335D

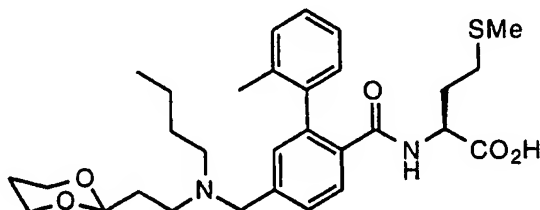
4-(N-(2-(1,3-dioxan-2-ylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoic acid,

17010 Following the procedure of example 1130D, example 1335C (310 mg, 0.72 mmol) provided 222 mg (75%) of the title compound. MS (ESI+): 412 (MH+); (ESI-): 410 (M-H).

Example 1335E

N-[4-(N-(2-(1,3-dioxan-2-ylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

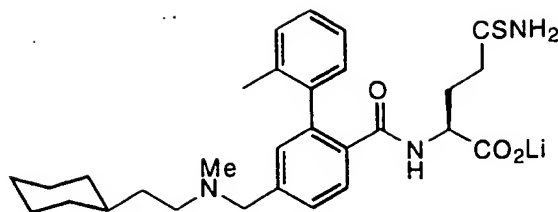
17015 Following the procedure of example 1178I, example 1335D (85 mg, 0.25 mmol) provided 57 mg (50%) of the title compound. MS (ESI+): 557 (MH+); (ESI-): 555 (M-H).

Example 1335F

N-[4-(N-(2-(1,3-dioxan-2-ylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

17025 Following the procedure of example 1104D, example 1335 E (55 mg (0.10 mmol) provided 30 mg of the title compound. ¹H nmr (300 MHz., CD₃OD): δ 7.64, d, 1H; 7.49, dd, 1H; 7.29, m, 1H; 7.02 - 7.22, m, 4H; 4.64, t, 1H; 4.29, m, 3H; 3.91, ddd, 2H; 3.66, dt, 2H; 3.22, m, 2H; 3.03, m, 2H; envelope 1.74 - 2.16, m, 12H; 1.62, m, 3H; 1.18 - 1.36, mn, 3H; 0.88, t, 3H. MS (ESI+): 543 (MH+); (ESI-): 541 (M-H). Calc'd for C₃₁H₄₃N₂O₅S•1.30 H₂O; C 63.64; H 7.94; N 4.95; Found: C 63.63; H 7.37; N 5.07.

17030

Example 1336

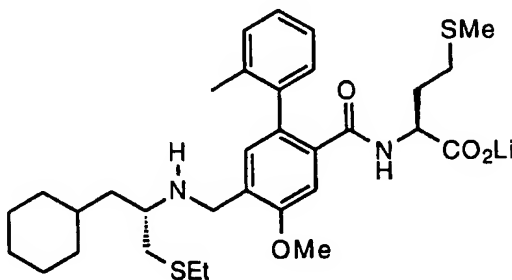
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]thioglutamine Lithium Salt

N-[4-(*N*-(2-cyclohexylethyl)-*N*-methylaminomethyl)-2-(2-methylphenyl)benzoyl]thioglutamine methyl ester (12 mg, 22.9 μ mol) was saponified using the standard LiOH procedure, evaporated, and lyophilized from water to provide 9.8 mg of the title compound. MS *m/e* 514 (M-H)⁻.

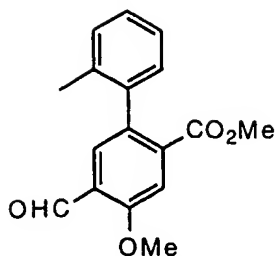
Example 1336B

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]thioglutamine Methyl Ester

N-[4-(*N*-(2-cyclohexylethyl)-*N*-methylaminomethyl)-2-(2-methylphenyl)benzoyl]glutaminitrile methyl ester, see Example 1041, (139 mg, 0.28 mmol) was dissolved in 5 mL pyridine with TEA (0.5 mL). Excess H₂S was bubbled into the solution which was then sealed and stirred at room temperature for 18 hours. The reaction was evaporated to dryness, dissolved in EtOAc, washed with water and brine, and chromatographed (50 % EtOAc/hexanes) to give 13 mg of the methyl ester. MS *m/e* 524 (M+H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 0.82 (m, 2H), 1.11 (m, 3H), 1.32 (m, 5H), 1.6 (m, 7H), 2.18 (m, 6H), 2.32 (m, 1H), 2.58 (m, 1H), 2.75 (m, 1H), 3.53 (m, 2H), 3.72 (s, 3H), 6.9-7.5 (m, 9H), 7.83 (m, 1H).

Example 1337

N-[4-(1-ethylthio-3-cyclohexylpropyl)-5-methoxy-2-(2-methylphenyl)benzoyl]methionine

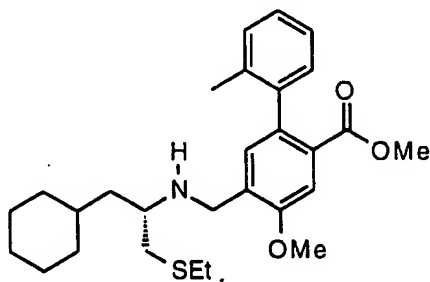


17060

Example 1337A2-(2-Methylphenyl)-4-formyl-5-methoxybenzoic acid, methyl ester

17065

A solution of example 1134D (180 mg, 0.63 mmol) in 2 mL of DMF was treated with sodium methoxide (102 mg, 1.89 mmol) and the mixture stirred for 3 hours. The solution was diluted with water and extracted with 3 portions of ethyl acetate. The combined organic extracts were washed with water, brine, dried filtered and concentrated. The residue was purified by column chromatography to provide 40g (22%) of the title compound. MS (DCI, NH₃): 302 (M+ NH₄⁺).



17070

Example 1337B4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-methoxy-2-(2-methylphenyl)benzoic acid, methyl ester

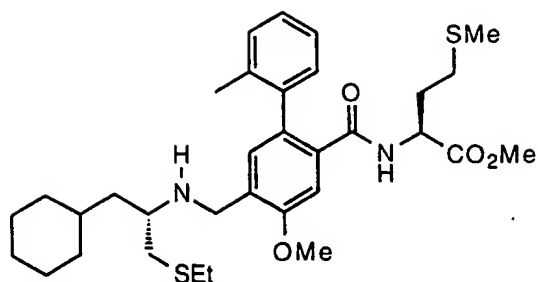
17075

Using the procedure of example 1134E, example 1337A provided the title compound. MS (ESI +): 470 (MH⁺); (ESI-) 468 (M-H).

Example 1337C4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-methoxy-2-(2-methylphenyl)benzoic acid

17080

Using the procedure of example 1134F, example 1337B provided the title compound. MS (ESI +): 456 (MH⁺); (ESI-) 454 (M-H).

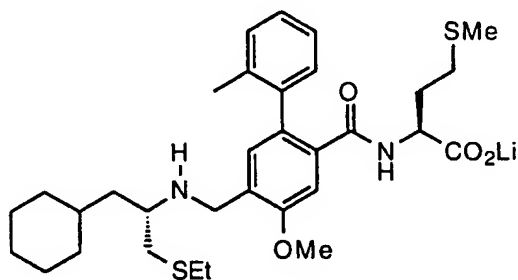
Example 1337D

17085

N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-methoxy-2-(2-methylphenyl)benzoyl]methionine, methyl ester

According to the procedure described in example 1178I, example 1137C (55 mg, 0.12 mmol) provided 39 mg (54%) of the title compound. MS (ESI +): 601 (MH⁺); (ESI-) 599 (M-H).

17090

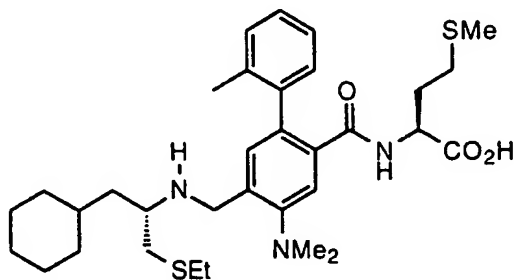
Example 1337

N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-methoxy-2-(2-methylphenyl)benzoyl]methionine

17095

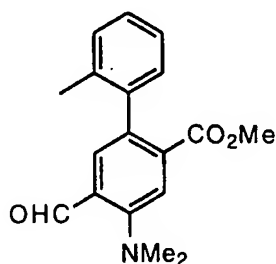
Following the procedure of example 1105D, example 1137D (39 mg, 0.065 mmol) provided the title compound. ¹H NMR (300 MHz, DMSO): δ 7.9 (1H), 7.0-7.3 (5H), 4.1 (1H), 3.9 (1H), 3.3 (3H), 2.7 (1H), 2.4 (3H), 2.0-2.3 (6H), 1.95 (3H), 0.8- 1.9 (22H). Mass spec (ESI): 587 (M+H), 585 (M-H)

17100

Example 1338

N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-N,N'-dimethylamino-2-(2-methylphenyl)benzoyl]methionine

17105

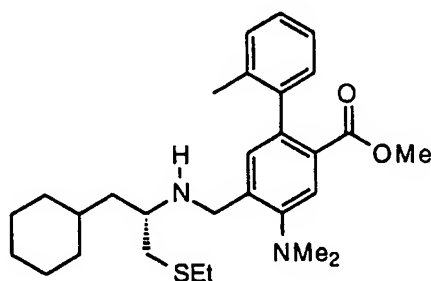


Example 1338A

2-(2-Methylphenyl)-4-formyl-5-N,N-dimethylaminobenzoic acid, methyl ester

17110 A solution of example 1134D (146 mg, 0.50 mmol) in 1 mL of DMF was treated with 2 mL of 40% aqueous dimethylamine and the mixture heated at 70°C for 2 days. The cooled reaction mixture was diluted with water and the pH of the mixture adjusted to 5. The solution was extracted with 3 portions of ethyl acetate and the combined organic extracts were washed with water and brine, dried, filtered and concentrated. The residue was dissolved in ethyl acetate and treated with ethereal diazomethane until TLC analysis indicated no more acid present. This solution was concentrated and the residue purified by column chromatography on silica gel (25 g, 15% ethyl acetate/hexanes) to provide 124 mg (87%) of the title compound. MS (DCI, NH₃): 298 (MH⁺).

17115

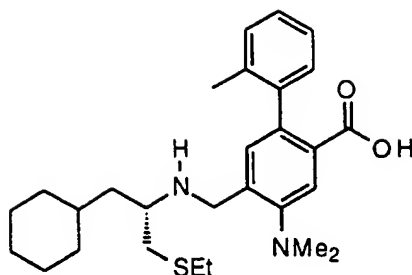


Example 1338B

4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-N,N'-dimethylamino-2-(2-methylphenyl)benzoic acid, methyl ester

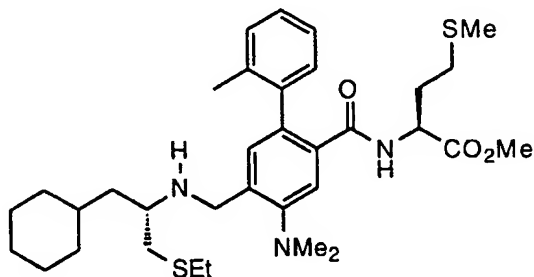
Using the procedure of example 1134E, example 1338A provided the title compound. MS (ESI⁺): 483 (MH⁺); (ESI⁻) 481 (M-H).

17125

Example 1338C

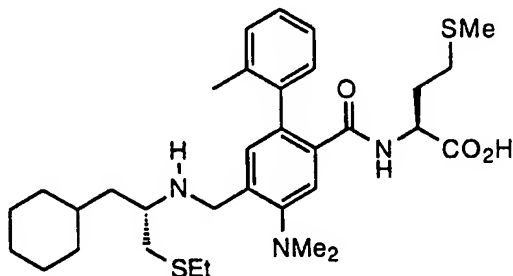
4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-N,N'-dimethylamino-2-(2-methylphenyl)benzoic acid

17130 Following the procedure of example 1134F, example 1138B provided the title compound. MS (ESI +): 469 (MH⁺); (ESI-) 467 (M-H).

Example 1338D

17135 N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-N,N'-dimethylamino-2-(2-methylphenyl)benzoyl]methionine, methyl ester

According to the procedure described in example 1178I, example 1138C (93 mg, 0.20 mmol) provided 69 mg (56%) of the title compound. MS (ESI +): 614 (MH⁺); (ESI-) 612 (M-H).

Example 1338E

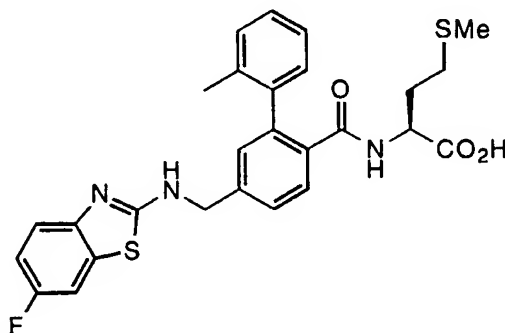
N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-N,N'-dimethylamino-2-(2-methylphenyl)benzoyl]methionine

17145 Following the procedure of example 1105D, example 1138D (69 mg, 0.11 mmol) provided the title compound. ¹H NMR (300 MHz., DMSO): δ 7.9 (1H), 7.0-7.3 (5H), 4.2 (1H), 3.9 (1H), 2.72 (6H), 2.45 (3H), 2.0-2.2 (6H), 1.9 (3H), 0.7-1.85 (22H). Mass spec (ESI): 600 (M+H), 598 (M-H).

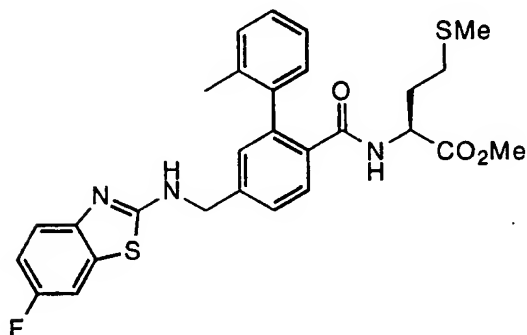
17150

Example 1339

Pittsburg example, waiting for experimental data and other information.



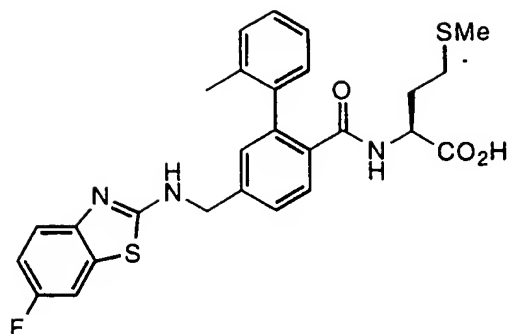
17155

Example 1340Example 1340A

17160 N-[4-N-(6-Fluorobenzothiazol-2-yl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

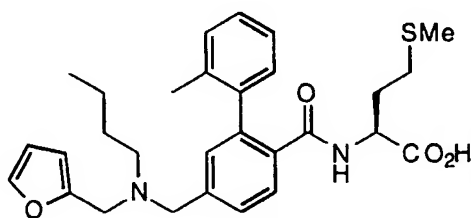
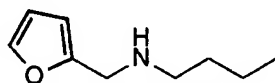
The desired compound was prepared according to the method of Example 1203A starting with N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester, prepared as in Example 403G, and 2-amino-6-fluorobenzothiazole. m/e (ESI) 538 (MH⁺)

17165

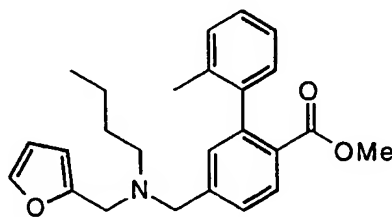
**Example 1340B***N*-[4-*N*-(6-Fluorobenzothiazol-2-yl)aminomethyl]-2-(2-methylphenyl)benzoyl]methionine

17170 The desired compound was prepared according to the method of Example 403I starting with the compound in Example 1340A. ¹H (300MHz, CDCl₃, δ) 7.91 (1H, m), 7.51 (1H, m), 7.34 (2H, m), 7.30-7.15 (4H, m), 7.05 (3H, m), 5.99 (1H, m), 4.59 (1H, m), 4.48 (2H, bd, J=8Hz), 2.20-1.80 (9H, m), 1.72 (1H, m). m/e (ESI) 522 (MH⁺) Anal.calc. for C₂₇H₂₆FN₃O₃S₂·0.25 H₂O C 61.40, H 5.06, N 7.96 Found C 61.38, H 4.56, N 7.73

17175

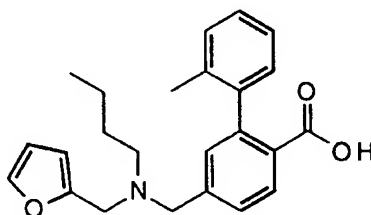
**Example 1341****Example 1341A***N*-Butyl-*N*-(furan-2-ylmethyl)amine

17180 The desired amine was prepared using the method described in Example 1171A starting with 2-furoic acid and butylamine. m/e (DCI/NH₃) 154 (MH⁺)

**Example 1341B**

4-(*N*-Butyl-*N*-(furan-2-ylmethyl)aminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester

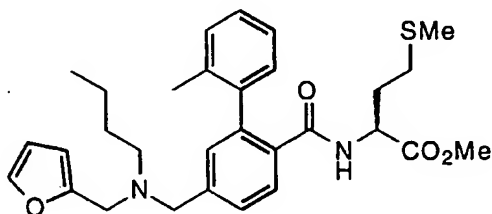
The desired compound was prepared using the method described in Example 1178G starting with *N*-Butyl-*N*-(furan-2-ylmethyl)amine, prepared as in Example 1341A, and 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as in Example 1178A-D. m/e (ESI) 392 (MH⁺)



Example 1341C

4-(*N*-Butyl-*N*-(furan-2-ylmethyl)aminomethyl)-2-(2-methylphenyl)benzoic acid

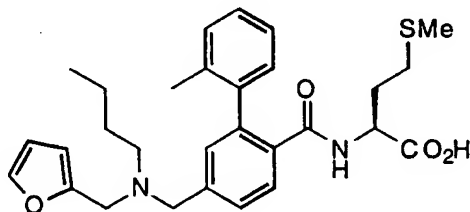
The desired acid was prepared using the method described in Example 403E starting with the compound prepared in Example 1341B.



Example 1341D

N-[4-(*N*-Butyl-*N*-(furan-2-ylmethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired product was prepared using the method described in Example 403F starting with the compound prepared in Example 1341C. m/e (ESI) 523 (MH⁺)



Example 1341E

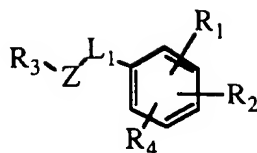
N-[4-(*N*-Butyl-*N*-(furan-2-ylmethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 403I starting with compound prepared in Example 1341D. ¹H (300MHz, CDCl₃, δ) 7.81 (1H,

d, J=8Hz), 7.57 (1H, m), 7.42 (1H, d, J=2Hz), 7.30-7.10 (5H, m), 6.35 (2H, m), 6.15 (1H, bd, J=8Hz), 4.43 (1H, m), 3.98 (2H, m), 3.90-3.75 (2H, m), 2.62 (2H, m), 2.20-2.00 (5H, m), 1.99 (3H, s), 1.95 (1H, m), 1.60 (3H, m), 1.29 (2H, m), 0.88 (3H, t, J=8Hz). m/e (ESI) 509 (MH⁺) Anal.calc. for C₂₉H₃₆N₂O₄S·0.50 H₂O C 67.28, H 7.20, N 5.41 Found C 67.42, H 6.96, N 5.44.

WHAT IS CLAIMED IS:

- 17220 1. A compound having Formula I

**I**

or a pharmaceutically acceptable salt thereof, wherein

- 17225 **R₁** is selected from the group consisting of

- (1) hydrogen,
- (2) alkenyl,
- (3) alkynyl,
- (4) alkoxy,
- 17230 (5) haloalkyl,
- (6) halogen,
- (7) loweralkyl,
- (8) thioalkoxy,
- (9) aryl-L₂- wherein aryl is selected from the group consisting of

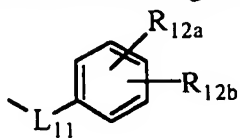
- 17235 (a) phenyl,
- (b) naphthyl,
- (c) dihydronaphthyl,
- (d) tetrahydronaphthyl,
- (e) indanyl, and
- 17240 (f) indenyl

wherein (a)-(f) are unsubstituted or substituted with at least one of X, Y,
or Z wherein X, Y, and Z are independently selected from the
group consisting of

- 17245 alkenyl,
- alkynyl,
- alkoxy,
- aryl,
- carboxy,
- cyano,
- 17250 halogen,
- haloalkyl,

- hydroxy,
hydroxyalkyl,
loweralkyl,
17255 nitro,
N-protected amino, and
-NRR' wherein R and R' are independently selected
from the group consisting of
hydrogen and
17260 loweralkyl,
oxo (=O), and
thioalkoxy and
L₂ is absent or is selected from the group consisting of
-CH₂-,
17265 -CH₂CH₂-,
-CH(CH₃)-,
-O-,
-C(O)-,
-S(O)_q wherein q is 0, 1 or 2, and
17270 -N(R)-, and
(10) heterocycle-L₂- wherein L₂ is as defined above and the heterocycle is
unsubstituted or substituted with 1, 2, 3 or 4 substituents
independently selected from the group consisting of
17275 (a) loweralkyl,
(b) hydroxy,
(c) hydroxyalkyl,
(d) halogen
(e) cyano,
(f) nitro,
17280 (g) oxo (=O),
(h) -NRR',
(i) N-protected amino,
(j) alkoxy,
(k) thioalkoxy,
17285 (l) haloalkyl,
(m) carboxy, and
(n) aryl;

R_2 is selected from the group consisting of



17290

(1)

wherein L_{11} is selected from the group

consisting of

- (a) a covalent bond,
- (b) $-C(W)N(R)-$ wherein R is defined previously and W is selected from the group consisting of O and S ,

17295

- (c) $-C(O)-$,
- (d) $-N(R)C(W)-$,
- (e) $-CH_2O-$,
- (f) $-C(O)O-$, and
- (g) $-CH_2N(R)-$,

17300

R_{12a} is selected from the group consisting of

- (a) hydrogen,
- (b) loweralkyl, and
- (c) $-C(O)OR_{13}$ wherein R_{13} is selected from the group consisting of

17305

hydrogen and

a carboxy-protecting group, and

R_{12b} is selected from the group consisting of

- (a) hydrogen and
- (b) loweralkyl,

17310

with the proviso that R_{12a} and R_{12b} are not both hydrogen,

(2) $-L_{11}-C(R_{14})(R_v)-C(O)OR_{15}$ wherein L_{11} is defined previously,

R_v is selected from the group consisting of

- (a) hydrogen and
- (b) loweralkyl,

17315

R_{15} is selected from the group consisting of

- (a) hydrogen,
- (b) alkanoyloxyalkyl,
- (c) loweralkyl, and

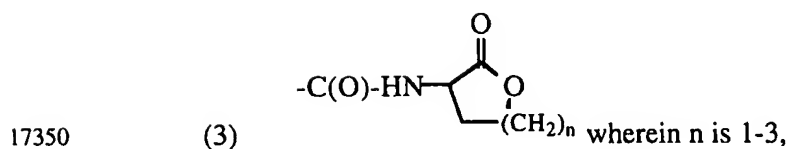
17320

(b) a carboxy-protecting group, and

R_{14} is selected from the group consisting of

- (a) alkoxyalkyl,

- 17325 (b) alkoxyarylalkyl,
(c) alkoxycarbonylalkyl,
(d) alkylsulfinylalkyl,
(e) alkylsulfonylalkyl,
(f) alkynyl,
(g) aminoalkyl,
(h) aminocarbonylalkyl,
17330 (i) aminothiocarbonylalkyl,
(j) aryl,
(k) arylalkyl,
(l) carboxyalkyl,
(m) cyanoalkyl,
17335 (n) cycloalkyl,
(o) cycloalkylalkoxyalkyl,
(p) cycloalkylalkyl,
(q) (heterocyclic)alkyl,
(r) hydroxyalkyl,
17340 (s) hydroxyarylalkyl,
(t) loweralkyl,
(u) sulfhydrylalkyl,
(v) thioalkoxyalkyl wherein the thioalkoxyalkyl is
unsubstituted or substituted with 1, 2, 3, or 4
17345 substituents selected from the group consisting of
halogen,
(w) thioalkoxyalkylamino, and
(x) thiocycloalkyloxyalkyl,



- (4) $-C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16}$ wherein R_{14} is defined previously
and R_{16} is selected from the group consisting of
17355 (a) loweralkyl,
(b) haloalkyl,
(c) aryl wherein the aryl is unsubstituted or substituted with

- 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR'
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl, and
- (d) heterocycle wherein the heterocycle is unsubstituted or substituted with substituents independently selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR',
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl;
- (5) $-C(O)NH-CH(R_{14})$ -tetrazolyl wherein the tetrazole ring is unsubstituted or substituted with loweralkyl or haloalkyl,

(6) $-L_{11}$ -heterocycle,

17395

(7) $-C(O)NH-CH(R_{14})-C(O)NR_{17}R_{18}$ wherein R_{14} is defined previously and R_{17} and R_{18} are independently selected from the group consisting of

17400

- (a) hydrogen,
- (b) loweralkyl,
- (c) arylalkyl,
- (d) hydroxy, and
- (e) dialkylaminoalkyl,

(8) $-C(O)OR_{15}$, and

17405

(9) $-C(O)NH-CH(R_{14})$ -heterocycle wherein R_{14} is as previously defined and the heterocycle is unsubstituted or substituted with loweralkyl or haloalkyl;

17410

L_1 is absent or is selected from the group consisting of

(1) $-L_4-N(R_5)-L_5-$ wherein L_4 is absent or selected from the group consisting of

17415

- (a) C_1 -to- C_{10} -alkylene and
- (b) C_2 -to- C_{16} -alkenylene,

wherein the alkylene and alkenylene groups are unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

17420

alkenyl,
alkenyloxy,
alkenyloxyalkyl,
alkenyl[S(O)_q]alkyl,
alkoxy,

17425

alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2 hydroxyl substituents, with the proviso that no two hydroxyls are attached to the same carbon,

17430

alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from the

- group consisting of
halogen and
cycloalkyl,
alkylsilyloxy,
17435 alkyl[S(O)_q],
alkyl[S(O)_q]alkyl,
aryl wherein the aryl is unsubstituted or substituted with
1, 2, 3, 4, or 5 substituents independently
selected from the group consisting of
17440 alkoxy wherein the alkoxy is unsubstituted or
substituted with substituents selected
from the group consisting of cycloalkyl,
aryl,
arylalkyl,
17445 aryloxy wherein the aryloxy is unsubstituted or
substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of,
halogen,
17450 nitro, and
-NRR',
cycloalkyl,
halogen,
loweralkyl,
17455 hydroxyl,
nitro,
-NRR', and
-SO₂NRR',
arylalkoxy wherein the arylalkoxy is unsubstituted or
17460 substituted with substituents selected from the
group consisting of alkoxy,
arylalkyl,
arylalkyl[S(O)_q]alkyl,
aryl[S(O)_q],
17465 aryl[S(O)_q]alkyl wherein the aryl[S(O)_q]alkyl is
unsubstituted or substituted with 1, 2, 3, 4, or 5
substituents independently selected from

- alkoxy and
loweralkyl,
17470 arylalkoxyalkyl wherein the arylalkoxyalkyl is
unsubstituted or substituted with substituents
selected from the group consisting of
alkoxy, and
halogen,
- 17475 aryloxy,
aryloxyalkyl wherein the aryloxyalkyl is unsubstituted or
substituted with substituents selected from the
group consisting of halogen,
carboxyl,
- 17480 $-C(O)NR_C R_D$ wherein R_C and R_D are independently
selected from the group consisting of
hydrogen,
loweralkyl, and
alkoxycarbonyl or
- 17485 R_C and R_D together with the nitrogen to which
they are attached form a ring selected
from the group consisting of
morpholine,
piperidine,
17490 pyrrolidine
thiomorpholine,
thiomorpholine sulfone, and
thiomorpholine sulfoxide,
wherein the ring formed by R_C and R_D
- 17495 together is unsubstituted or
substituted with 1 or 2
substituents independently
selected from the group consisting
of alkoxy and alkoxyalkyl,
- 17500 cycloalkenyl wherein the cycloalkenyl is unsubstituted or
substituted with 1 or 2 substituents selected from
the group consisting of alkenyl,
cyclolalkoxy,
cycloalkoxycarbonyl,

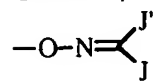
- 17505 cycloalkoxyalkyl,
 cycloalkyl wherein the cycloalkyl is unsubstituted or
 substituted with 1, 2, 3, 4, or 5 substituents
 independently selected from the group consisting
 of aryl,
17510 loweralkyl, and
 alkanoyl,
 cycloalkylalkoxy,
 cycloalkylalkoxycarbonyl,
 cycloalkylalkoxyalkyl,
17515 cycloalkylalkyl,
 cycloalkyl[S(O)_q]alkyl,
 cycloalkylalkyl[S(O)_q]alkyl,
 fluorenyl,
 heterocycle wherein the heterocycle is unsubstituted or
17520 substituted with 1, 2, 3, or 4 substituents
 independently selected from the group
 consisting of
 alkoxy wherein the alkoxy is unsubstituted or
 substituted with 1 or 2 substituents
17525 independently selected from the group
 consisting of aryl and cycloalkyl,
 alkoxyalkyl wherein the alkoxyalkyl is
 unsubstituted or substituted with 1 or 2
 substituents independently selected from
17530 the group consisting of
 aryl and
 cycloalkyl,
 alkoxycarbonyl wherein the alkoxycarbonyl is
 unsubstituted or substituted with 1 or 2
17535 substituents independently selected from
 the group consisting of
 aryl and
 cycloalkyl,
 aryl wherein the aryl is unsubstituted or
17540 substituted with 1, 2, 3, 4, or 5
 substituents independently selected from

- the group consisting of
alkanoyl,
alkoxy,
17545 carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
nitro,
17550 -NRR', and
thioalkoxy,
arylalkyl,
aryloxy,
cycloalkoxyalkyl,
17555 cycloalkyl,
cycloalkylalkyl,
halogen,
heterocycle,
hydroxyl,
17560 loweralkyl wherein the loweralkyl is
unsubstituted or substituted with 1, 2, or
3 substituents independently selected
from the group consisting of
heterocycle,
17565 hydroxyl,
with the proviso that no two hydroxyls
are attached to the same carbon,
and
-NRR³R^{3'} wherein R³ and R^{3'} are
17570 independently selected from the
group consisting of
hydrogen
aryl,
loweralkyl,
17575 aryl,
arylalkyl,
heterocycle,
(heterocyclic)alkyl,

	cycloalkyl, and
17580	cycloalkylalkyl, and
	sulphydryl,
	(heterocyclic)alkoxy,
	(heterocyclic)alkyl,
	(heterocyclic)alkyl[S(O) _q]alkyl,
17585	(heterocyclic)oxy,
	(heterocyclic)alkoxyalkyl,
	(heterocyclic)oxyalkyl,
	heterocycle[S(O) _q]alkyl,
	hydroxyl,
17590	hydroxyalkyl,
	imino,
	N-protected amino,
	=N-O-aryl, and
	=N-OH,
17595	=N-O-heterocycle wherein the heterocycle is
	unsubstituted or substituted with 1, 2, 3, or 4
	substituents independently selected from the
	group consisting of
	loweralkyl,
17600	hydroxy,,
	hydroxyalkyl,
	halogen,
	cyano,
	nitro,
17605	oxo (=O),
	-NRR'
	N-protected amino,
	alkoxy,
	thioalkoxy,
17610	haloalkyl,
	carboxy, and
	aryl,
	=N-O-loweralkyl,
	-NR ^{R3} R ^{R3'} ,
17615	-NHNRC _{RD} ,

-OG wherein G is a hydroxyl protecting group,

-O-NH-R,



wherein J and J' are independently selected

from the group consisting of

17620 loweralkyl and
arylalkyl,

oxo,

oxyamino(alkyl)carbonylalkyl,

oxyamino(arylalkyl)carbonylalkyl,

17625 oxyaminocarbonylalkyl,

-SO₂-A wherein A is selected from the group

consisting of

loweralkyl,

aryl, and

17630 heterocycle

wherein the loweralkyl, aryl, and heterocycle are

unsubstituted or substituted with 1, 2, 3,

4, or 5 substituents independently

selected from the group consisting of

17635 alkoxy,

halogen,

haloalkyl,

loweralkyl, and

nitro,

17640 sulfhydryl,

thioxo, and

thioalkoxy,

L₅ is absent or selected from the group consisting of

(a) C₁-to-C₁₀-alkylene and

17645 (b) C₂-to-C₁₆-alkenylene

wherein (a) and (b) are unsubstituted or substituted as

defined previously, and

R₅ is selected from the group consisting of

hydrogen,

17650 alkanoyl wherein the alkanoyl is unsubstituted or

substituted with substituents selected from the

- group consisting of aryl,
alkoxy,
alkoxyalkyl,
17655 alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1, 2 or 3
substituents independently selected from the
group consisting of
aryl and
17660 halogen,
alkylaminocarbonylalkyl wherein the
alkylaminocarbonylalkyl is unsubstituted or
substituted with 1 or 2 substituents
independently selected from the group consisting
17665 of aryl,
(anthracenyl)alkyl,
aryl,
arylalkoxy,
arylalkyl wherein the arylalkyl is unsubstituted or
17670 substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group
consisting of
alkoxy,
aryl,
17675 carboxyl,
cyano,
halogen,
haloalkoxy,
haloalkyl,
17680 nitro,
oxo, and
-L₁₁-C(R₁₄)(R_v)-C(O)OR₁₅,
(aryl)oyl wherein the (aryl)oyl is unsubstituted or
substituted with substituents selected from the
17685 group consisting of halogen,
aryloxycarbonyl,
carboxaldehyde,
-C(O)NRR',

- 17690 cycloalkoxycarbonyl,
cycloalkylaminocarbonyl,
cycloalkylaminothiocarbonyl,
cyanoalkyl,
cycloalkyl,
cycloalkylalkyl wherein the cycloalkylalkyl is
- 17695 unsubstituted or substituted with 1 or 2 hydroxyl
substituents,
with the proviso that no two hydroxyls are attached to the
same carbon,
(cycloalkyl)oyl,
- 17700 (9,10-dihydroanthracenyl)alkyl wherein the
(9,10-dihydroanthracenyl)alkyl is unsubstituted
or substituted with 1 or 2 oxo substituents,
haloalkyl,
heterocycle,
- 17705 (heterocyclic)alkyl wherein the (heterocyclic)alkyl is
unsubstituted or substituted with 1, 2, 3, 4, or 5
substituents selected from the group consisting of
loweralkyl,
(heterocyclic)oyl,
- 17710 loweralkyl, wherein the loweralkyl is unsubstituted
or substituted with substituents selected from the
group consisting of -NRR',
-SO₂-A, and
thioalkoxyalkyl;
- 17715
- (2) -L₄-O-L₅-,
- (3) -L₄-S(O)_m-L₅- wherein L₄ and L₅ are defined previously and m is 0, 1,
or 2,
- 17720
- (4) -L₄-L₆-C(W)-N(R₆)-L₅- wherein L₄, W, and L₅ are defined previously,
R₆ is selected from the group consisting of
- (a) hydrogen,
- (b) loweralkyl,
- 17725 (c) aryl,

- 17730 (d) arylalkyl,
 (e) heterocycle,
 (f) (heterocyclic)alkyl,
 (g) cyclolakyl, and
 (h) cycloalkylalkyl, and
 L_6 is absent or is selected from the group consisting of
 (a) -O-,
 (b) -S-, and
 (c) -N(R₆)- wherein R₆ is selected from the group
- 17735 consisting of
 hydrogen,
 loweralkyl,
 aryl,
 arylalkyl,
 heterocycle,
 17740 (heterocyclic)alkyl,
 cyclolakyl, and
 cycloalkylalkyl,
- 17745 (5) -L₄-L₆-S(O)_m-N(R₅)-L₅-,
 (6) -L₄-L₆-N(R₅)-S(O)_m-L₅-,
 (7) -L₄-N(R₅)-C(W)-L₇-L₅- wherein L₄, R₅, W, and L₅ are
 17750 defined previously and L₇ is absent or is selected from the group
 consisting of -O- and -S-,
 (8) C₁-C₁₀-alkylene wherein the alkylene group is unsubstituted or
 substituted with 1 or 2 substituents independently selected from
 17755 the group consisting of
 (a) aryl,
 (b) arylalkyl,
 (c) heterocycle,
 (d) (heterocyclic)alkyl,
 17760 (e) cyclolakyl,
 (f) cycloalkylalkyl,
 (g) alkylthioalkyl, and

(h) hydroxy,

17765 (9) C₂-to-C₁₀-alkenylene wherein the alkenylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

(a) aryl,

(b) arylalkyl,

17770 (c) (aryl)oxyalkyl wherein the (aryl)oxyalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,

(d) heterocycle,

17775 (e) (heterocycle)alkyl,

(f) hydroxyalkyl,

(g) cyclolalkyl,

(h) cycloalkylalkyl,

(i) alkylthioalkyl, and

17780 (j) hydroxy,

(10) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

17785 (a) aryl,

(b) arylalkyl,

(c) heterocycle,

(d) (heterocyclic)alkyl,

(e) cyclolalkyl,

17790 (f) cycloalkylalkyl,

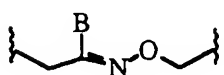
(g) alkylthioalkyl, and

(h) hydroxy,

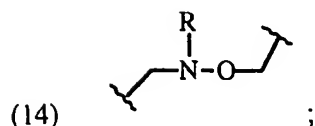
(11) -L₄-heterocycle-L₅-,

17795

(12) a covalent bond,

(13)  wherein B is selected from the group consisting of

loweralkyl and
arylalkyl, and



Z is selected from the group consisting of

- (1) a covalent bond,
- (2) -O-,
- (3) -S(O)_q-, and
- (4) -NR_Z- wherein R_Z is selected from the group consisting of
 - (a) hydrogen
 - (b) loweralkyl,
 - (c) aryl,
 - (d) arylalkyl,
 - (e) heterocycle,
 - (f) (heterocyclic)alkyl,
 - (g) cyclolalkyl, and
 - (h) cycloalkylalkyl;

R₃ is selected from the group consisting of

- (1) hydrogen,
- (2) aryl,
- (3) fluorenyl,
- (4) heterocycle,

with the proviso that the heterocycle is other than imidazole and pyridine,

wherein (2)-(4) are unsubstituted or substituted with 1, 2, 3, 4, or 5

substituents independently selected from the group consisting of

- (a) alkanoyl,
- (b) alkoxy wherein the alkoxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
 - halogen,
 - aryl, and
 - cycloalkyl,
- (c) alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2, 3, 4 or 5 substituents

- 17835 independently selected from the group consisting of
aryl and
cycloalkyl,
- (d) alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of
17840 aryl, and
cycloalkyl,
- (e) alkylsilyloxyalkyl,
- (f) arylalkyl,
- (g) aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3,
17845 4, or 5 substituents independently selected from the
group consisting of
alkanoyl,
alkoxy wherein the alkoxy is unsubstituted or substituted
with 1 or 2 substituents selected from the group
17850 consisting of cycloalkyl,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
17855 nitro,
-NRR', and
thioalkoxy,
- (h) arylalkyl,
- (i) aryloxy wherein the aryloxy is unsubstituted or
17860 substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of,
halogen,
nitro, and
-NRR',
- 17865 (j) (aryl)oyl,
- (k) carboxaldehyde,
- (l) carboxy,
- (m) carboxyalkyl,
- (n) -C(O)NRR" wherein R is defined previously and R" is
17870 selected from the group consisting of

- hydrogen,
loweralkyl, and
carboxyalkyl,
- 17875 (o) cyano,
(p) cyanoalkyl,
(q) cycloalkyl,
(r) cycloalkylalkyl,
(s) cycloalkoxyalkyl,
(t) halogen,
- 17880 (u) haloalkyl wherein the haloalkyl is unsubstituted or substituted
with 1, 2, 3, 4, or 5 hydroxyl substituents,
with the proviso that no two hydroxyls are attached to the same
carbon,
- 17885 (v) heterocycle,
(w) hydroxyl,
(x) hydroxyalkyl wherein the hydroxyalkyl is unsubstituted or
substituted with substituents selected from the group
consisting of aryl,
- 17890 (y) loweralkyl wherein the loweralkyl is unsubstituted or substituted
with substituents selected from the group consisting of
heterocycle,
hydroxyl,
with the proviso that no two hydroxyls are attached to the
same carbon,
- 17895 -NR^{R3}R^{R3'}, and
-P(O)(OR)(OR'),
- (z) nitro,
(aa) -NRR',
(bb) oxo,
- 17900 (cc) -SO₂NR_AR_B' wherein R_A' and R_B' are independently selected
from the group consisting of
hydrogen,
(aryl)oyl,
loweralkyl, and
- 17905 heterocycle wherein the heterocycle is unsubstituted or
substituted with 1, 2, or 3 substituents
independently selected from the group consisting

of loweralkyl,

(dd) sulfhydryl, and

17910

(ee) thioalkoxy,

(5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from the group consisting of

(a) alkoxy,

17915

(b) aryl,

(c) arylalkoxy

(d) aryloxy wherein the aryloxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,

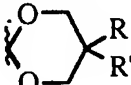
17920

(e) loweralkyl,

(f) halogen,

(g) $\text{NRR}^3\text{RR}^{3'}$,

(h) oxo, and

(i) ,

17925

(6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

(a) loweralkyl,

17930

(b) alkoxy,

(c) halogen,

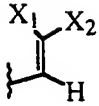
(d) aryl,

(e) aryloxy,

(f) alkanoyl, and

17935

(g) $\text{NRR}^3\text{RR}^{3'}$,

(7)  wherein X_1 and X_2 together are cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of aryl, and

17940

(8) $-\text{P(W)}\text{RR}^3\text{RR}^{3'}$; and

R₄ is selected from the group consisting of

- 17945 (1) hydrogen,
 (2) loweralkyl,
 (3) haloalkyl
 (4) halogen,
 (5) aryl,
 (6) arylalkyl,
 17950 (7) heterocycle,
 (8) (heterocyclic)alkyl
 (9) alkoxy, and
 (10) -NRR'; or

L₁, Z, and R₃ together are selected from the group consisting of

- 17955 (1) aminoalkyl,
 (1) haloalkyl,
 (2) halogen,
 (3) carboxaldehyde, and
 17960 (4) (carboxaldehyde)alkyl, and
 (5) hydroxyalkyl,

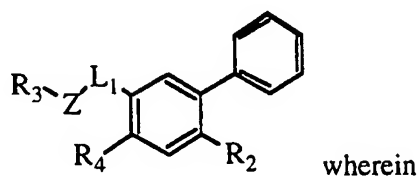
with the proviso that when **L₁, Z, and R₃** together are (1)-(5), **R₁** is other than hydrogen.

2. A compound according to claim 1 wherein **L₁** is selected from the group consisting of

- (1) -L₄-N(R₅)-L₅-,
 (2) -L₄-L₆-C(W)-N(R₆)-L₅-, and
 5 (3) -L₄-N(R₅)-C(W)-L₇-L₅- and

Z is a covalent bond or -O-.

3. A compound according to claim 1 of formula



R₃ is selected from the group consisting of

- (1) hydrogen,
- (2) aryl,
- (3) heterocycle,
- (3) fluorenyl,

wherein (2)-(4) are unsubstituted or substituted as defined previously,

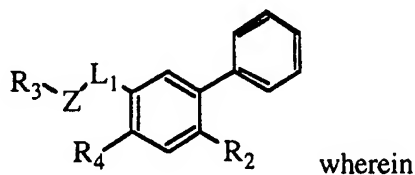
- (4) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and
- (5) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously;

L₁ is selected from the group consisting of

- (1) -L₄-N(R₅)-L₅⁻,
- (2) -L₄-L₆-C(W)-N(R₆)-L₅⁻, and
- (3) -L₄-N(R₅)-C(W)-L₇-L₅⁻; and

Z is a covalent bond or -O-.

4. A compound according to claim 1 of formula



R₃ is selected from the group consisting of

- (1) hydrogen,
- (2) aryl,
- (3) fluorenyl,

wherein (2) and (3) are unsubstituted or substituted as defined previously,

- (4) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and
- (5) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously;

L₁ is selected from the group consisting of

- (1) -L₄-N(R₅)-L₅⁻,
- (2) -L₄-L₆-C(W)-N(R₆)-L₅⁻, and

(3) $-L_4-N(R_5)-C(W)-L_7-L_5-$; and

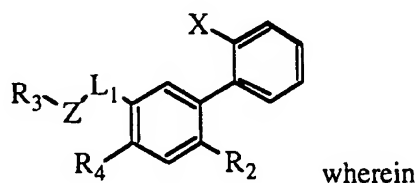
Z is a covalent bond or -O-.

20

5. A compound according to claim 4 selected from the group consisting of
- [4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine,
 - [4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine,
 - [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine,
 - 5 methyl ester, hydrochloride,
 - [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine,
 - [4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine,
 - hydrochloride,
 - [4-(4-hydroxy-prolinyl)amino-2-phenylbenzoyl]methionine, trifluoroacetate,
 - 10 [4-((2S,4S)-4-mercaptopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]-
 - methionine, trifluoroacetate,
 - [4-((2S,4R)-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]-
 - methionine, hydrochloride,
 - [4-((2S,4S)-4-thiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]-methionine,
 - 15 hydrochloride,
 - [4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine,
 - trifluoroacetate,
 - [4-(piperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine,
 - hydrochloride,
 - 20 [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine,
 - [4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine,
 - [4-(3-piperidinecarboxyamino)-2-phenylbenzoyl]methionine,
 - hydrochloride,
 - [4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-
 - 25 phenylbenzoyl]methionine, sodium salt,
 - [4-(2-piperazinylmethylamino)-2-phenylbenzoyl]methionine,
 - [4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine lithium salt,
 - N-[4-N-2-hydroxyethylamino-2-phenylbenzoyl]methionine,
 - N-[4-(N-2-amino-3-benzoyloxypropionyl)amino-2-phenylbenzoyl]methionine,
 - 30 N-[4-N-phenyl-N-benzylaminomethyl-2-phenylbenzoyl]methionine,
 - N-[4-N-(2-hydroxyethyl)-N-benzylaminomethyl-2-
 - phenylbenzoyl]methionine, lithium salt,

- 35 N-[4-N-(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,
 N-[4-N,N-dibenzylaminomethyl-2-phenylbenzoyl]methionine, lithium salt,
 N-[4-N-(benzyl-N-thiazol-5-ylmethyl)aminomethyl-2-phenylbenzoyl]-
 methionine,
 N-[4-(N-benzylaminomethyl)-2-phenylbenzoyl]methionine, hydrochloride salt,
 N-[4-(4-hydroxyprolinylamino)-2-phenylbenzoyl]methionine,
 N-[4-((2S,4S)-4-thiolpyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine,
 40 N-[4-((2S,4R)-4-thiolpyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine, and
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]-
 methionine, lithium salt.

6. A compound according to claim 1 of formula



R₃ is selected from the group consisting of

- 5 (1) hydrogen,
 (2) aryl,
 (3) fluorenyl,
 (4) heterocycle

wherein (2)-(4) are unsubstituted or substituted as defined previously,

- 10 (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as
 defined previously, and
 (6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as
 defined previously;

15 **L₁** is selected from the group consisting of

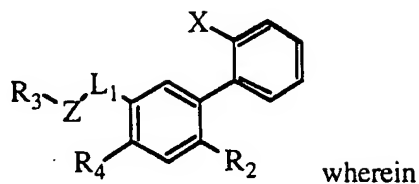
- (1) -L₄-N(R₅)-L₅-,
 (2) -L₄-L₆-C(W)-N(R₆)-L₅-, and
 (3) -L₄-N(R₅)-C(W)-L₇-L₅-;

20 **Z** is a covalent bond or -O-; and

X is selected from the group consisting of
 alkoxy,

25 aryl,
 25 carboxy,
 cyano,
 halogen,
 haloalkyl,
 hydroxy,
 30 hydroxyalkyl,
 loweralkyl,
 nitro,
 N-protected amino,
 -NRR,
 35 oxo (=O), and
 thioalkoxy.

7. A compound according to claim 1 of formula



R₃ is selected from the group consisting of

- 5 (1) hydrogen,
 (2) aryl,
 (3) fluorenyl,
 wherein (2) and (3) are unsubstituted or substituted as defined previously,
 (4) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as
 10 defined previously, and
 (5) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as
 defined previously;

L₁ is selected from the group consisting of

- 15 (1) -L₄-N(R₅)-L₅-,
 (2) -L₄-L₆-C(W)-N(R₆)-L₅-, and
 (3) -L₄-N(R₅)-C(W)-L₇-L₅-;

Z is a covalent bond or -O-; and

20

X is selected from the group consisting of

- alkoxy,
- aryl,
- carboxy,
- 25 cyano,
- halogen,
- haloalkyl,
- hydroxy,
- hydroxyalkyl,
- 30 loweralkyl,
- nitro,
- N-protected amino,
- NRR,
- oxo (=O), and
- 35 thioalkoxy.

8. A compound according to claim 6 wherein X is selected from the group consisting of loweralkyl, halogen, and haloalkyl.

9. A compound according to claim 8 selected from the group consisting of
 - [4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine,
 - 4-(N-benzyl-N-phenyl)-aminomethyl-2-(2-methylphenyl)benzoylmethionine,
 - 5 N-[4-N-(2,2-dibenzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]-methionine, sodium salt,
 - N-[4-N-(2-benzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]-methionine, sodium salt,
 - N-[4-N-(2-cyclohexylmethyl-3-hydroxypropyl)amino-2-(2-methylphenyl)-benzoyl]methionine,
 - 10 N-[4-N-(furan-2-ylmethyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
 - N-[4-N-(2-benzylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
 - N-[4-N-(2-phenyl)ethyl-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
 - 15 N-[4-N-(3-phenyl)propyl-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
 - N-[4-N-(2,2-diphenyl)ethyl-N-phenyl)aminomethyl-2-(2-methylphenyl)-

benzoyl]methionine,
20 N-[4-N-(adamantan-1-ylmethyl)-N-phenyl]aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-(2-adamantan-1-ylethyl)-N-phenyl]aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N,N-dibenzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine,
25 lithium salt,
N-[4-N-(2-phenylethyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-(3-phenoxybenzyl)-N-benzylaminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
30 N-[4-N-methyl-N-(2-phenylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-benzyl-N-pyrazin-2-ylaminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-(2-phenylethyl)-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)-
35 benzoyl]methionine, lithium salt,
N-[4-N-(2-indol-3-ylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-(2-cyclohexyl-1-ethan-1-ol-2-yl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
40 N-[4-N-(1,3-diphenylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(1-cyclohexyl-6-methylhept-3-en-2-yl)aminomethyl-2-(2-methyl-
45 phenyl)benzoyl]methionine, lithium salt,
N-[4-N-(1-cyclohexyl-6-methylheptan-2-yl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(1-cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl)aminomethyl-
2-(2-methylphenyl)benzoyl]methionine,
50 N-[4-N-(1-cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl)aminomethyl-
2-(2-methylphenyl)benzoyl]methionine,
N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-methylphenyl)-
55 benzoyl]methionine, methyl ester,

- N-[4-N-phenylacetyl-amino-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-N-(4'-methylphenylacetyl)amino-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
60 N-[4-N-(4'-methoxyphenylacetyl)amino-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-(3-phenylpropionoyl)amino-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-N-(3-(2-methoxyphenyl)propionoyl)amino-2-(2-methylphenyl)benzoyl]-
65 methionine, lithium salt,
N-[4-N-benzyl-N-(thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-benzyl-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
70 N-[4-(2-cyclohexylethan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-benzyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-
75 methionine, trifluoroacetate salt,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-acetyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
80 N-[4-(N-(N,N-dimethylaminocarbonyl)-N-(2-cyclohexylethyl)-
aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-methanesulfonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-benzenesulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-
85 methylphenyl)benzoyl]methionine lithium salt,
N-[4-(3-cyclohexylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(4-cyclohexylbutan-3-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
90 N-[4-(6-cyclohexylhexan-5-ylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(1,2-dicyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-

methionine, lithium salt,
N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-
95 methionine,
N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, trifluoroacetate salt,
N-[4-(2-cyclohexylprop-1-en-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
100 N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]-2-amino-4-methanesulfonylbutanoic acid, lithium salt,
N-[4-(3-cyclohexyl-1-t-butylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)-
105 benzoyl]methionine, lithium salt,
N-[4-(3-cyclohexyl-1-phenylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-benzoyl-N-2-cyclohexylethylaminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
110 N-[4-N-t-butyloxycarbonyl-N-2-cyclohexylethylaminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
pivaloyloxymethyl N-[4-N-(3-cyclohexyl-1-ethylthioprop-2-yl)-N-methyl-
aminomethyl-2-(2-methylphenyl)benzoyl]methionine, hydrochloride salt,
N-[4-N-(3-cyclohexyl-1-ethylthioprop-2-yl)-N-methylaminomethyl-2-
115 (2-methylphenyl)benzoyl]-N-methylmethionine, lithium salt,
N-[4-N-(3-cyclohexyl-1-cyclohexylthioprop-2-yl)-N-methylamino-
methyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(3-cyclohexyl-1-(2-methylphenyl)thioprop-2-yl)-N-methyl-
aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
120 N-[4-N-(N-phenyl-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-toluenesulfonylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(3-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)-
125 benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzenesulfonyl)aminomethyl)-
2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-chlorobenzyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,

- 130 N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,
N-[4-(1-ethoxycarbonylpiperidin-4-ylaminomethyl)-2-(2-methylphenyl-benzoyl]methionine, lithium salt,
- 135 N-[4-(N-[3-methylthio-1-carboxyprop-2-yl]aminocarbonyl)-2-phenylbenzoyl]-methionine,
N-[4-N-(furan-2-ylmethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(furan-3-ylmethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 140 N-[4-N-benzyl-N-3-methoxyphenylaminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(2-phenylethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 145 N-[4-N-benzyl-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-N-(1,3-benzodiox-5-yl)-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(1,3-benzodiox-5-yl)-N-pyridizin-2-ylaminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 150 N-[4-(N-benzyl-N-(2-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(4-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 155 N-[4-(N-benzyl-N-(4-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(N-benzyl-N-(3-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(N-benzyl-N-(4-nitrophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]-methionine, lithium salt,
- 160 N-[4-N-(N-benzyl-N-(2-acetylphenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-benzyl-N-(3-acetylphenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 165 N-[4-N-(N-benzyl-N-(2-chlorophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,

- N-[4-N-(N-benzyl-N-(3-chlorophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 170 N-[4-N-(N-benzyl-N-(4-chlorophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-(N-benzyl-N-(2-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
- N-[4-(N-benzyl-N-(2-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 175 N-[4-(N-benzyl-N-(3-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-(N-benzyl-N-(4-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 180 N-[4-(N-benzyl-N-(4-trifluoromethylphenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(4-piperidin-1-ylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
- N-[4-N-(4-morpholin-1-ylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
- 185 N-[4-N-(4-phenoxyphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
- N-[4-N-(benzyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine,
- N-[4-N-(toluenesulfonyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- 190 N-[4-N-(methanesulfonyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(N-2-cyclohexylethyl-N-cyclopropylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine,
- 195 N-[4-(N-tetrahydrothiopyran-4-yl-N-thiazol-5-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-t-butyloxycarbonyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(3-cyclohexyl-1-oxo-1-piperidin-1-ylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 200 N-[4-(N-(1-ethylthio-4-methylpentan-2-yl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine,
- N-[4-(N-(1-ethylthio-4-methylpentan-2-yl)-N-methylaminomethyl)-2-(2-

- 205 methylphenyl)benzoyl]methionine,
N-[4-(N-(1,3-dicyclohexylpropan-2-yl)-N-methylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-(N-(1,3-dicyclohexylpropan-2-yl)-N-methylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine,
210 N-[4-(N-acetyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-(N-benzoyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-(N-benzenesulfoyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine,
215 N-[4-(N-(N,N-dibutylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(N-(N,N-dibutylacetamido)-N-methylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(N-(N,N-dibenzylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]-
220 methionine,
N-[4-(N-(2-cyclohexylethyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(N-butanesulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine,
225 N-[4-(N,N-dibutylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-butanesulfonyl-N-(3-phenylpropyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
230 N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-methylaminomethyl-2-
(2-methylphenyl)benzoyl]methionine, hydrochloride,
N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-isobutylaminomethyl-
2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-formylaminomethyl-2-
235 (2-methylphenyl)benzoyl]methionine,
N-[4-N-acetyl-N-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-N-t-butyloxycarbonyl-N-(3-cyclohexyl-1-ethylthiopropyl)amino-
methyl-2-(2-methylphenyl)benzoyl]methionine,
240 N-[4-N-benzoyl-N-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-

methylphenyl)-benzoyl]methionine,
N-[4-N-butanefulfoyl-N-(3-cyclohexyl-1-ethylthiopropyl)-2-yl]amino-
methyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-benzenesulfonyl-N-(3-cyclohexyl-1-ethylthiopropyl)-2-yl]amino-
245 methyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-5-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-
2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-methyl-N-(1,1-dimethyl-2-phenylethyl)aminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
250 N-[4-(N-methyl-N-(1,1-dimethyl-2-cyclohexylethyl)aminomethyl)-2-(2-
methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-2-cyclohexylethyl-N-thiazol-5-ylmethylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-(1-ethylthio-4-phenylbut-2-oxymethyl)-2-(2-methylphenyl)-benzoyl]-
255 methionine,
N-[4-N-benzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-benzyl-N-(4-carboxamidophenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
260 N-[4-N-benzyl-N-(4-sulfonamidophenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-N-benzoylsulfonamidophenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-propionylphenyl)aminomethyl-2-(2-methylphenyl)-
265 benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-benzoylphenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-(6-methylbenzthiazol-2-yl)phenyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
270 N-[4-N-2,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-2,4-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methyl-
275 phenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-vinylphenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,

- N-[4-N-3,5-difluorobenzyl-N-(4-acetylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 280 N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxy-1-phenylmethyl)phenyl)-aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 285 N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-3,5-difluorobenzyl-N-(4-(2-tert-butyl dimethylsiloxyethyl)phenyl)-aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-3,5-difluorobenzyl-N-(1-ethylthio-3-cyclohexylprop-2-yl)amino-methyl-2-(2-methylphenyl)benzoyl]methionine,
- 290 N-[4-(2-N-piperidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-N-2-methoxymethylpyrrolidin-1-ylaminoethenyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(4-trans-pentafluorophenoxy)cyclohexyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- 295 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]glutamine, trifluoroacetic acid salt,
- N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]homocysteine, lithium salt,
- 300 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]histidine, trifluoroacetic acid salt,
- N-[4-(N-cyclohexylmethylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(N,N-di-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
- 305 N-[4-(N-cyclohexylmethyl-N-phenylacetylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-(N-cyclohexylmethyl-N-1-adamantanoylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 310 N-[4-(N-cyclohexylmethyl-N-t-butoxycarbonylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-(N-cyclohexylmethyl-N-2-ethylhexyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(N-cyclohexylmethyl-N-2,2,2-trichloroethoxycarbonylaminoethyl)-2-(2-

- 315 methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-cyclohexyloxycarbonylaminoethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-adamantyloxycarbonylaminoethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
- 320 N-[4-(N-cyclohexylmethyl-N-phenoxy carbonylaminoethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-benzyloxycarbonylaminoethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-adamant-1-aminocarbonylaminoethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
- 325 N-[4-(N-cyclohexylmethyl-N-adamant-1-aminothiocabonylaminoethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
benzoyl]glutaminitrile, lithium salt,
- 330 N-[4-(N-p-toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-(4-benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)-
aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
- 335 (2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
(2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-
methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
- 340 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
benzoyl]norleucine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
(2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)-
benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
- 345 N-[4-(N-(2-cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
- 350 N-[4-(N-(2-cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,

- N-[4-(N-(2-cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 355 N-[4-(N-(2-cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(N-(2-cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(N-(2-cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 360 N-[4-(3-cyclohexyl-1-methoxyprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- (2S)-2-N-[4-(1-ethylsulfenyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfenylbutanoate, lithium salt,
- 365 N-[4-(N-(3-cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(N-glucosaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 370 (2S)-2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-difluoromethylthiobutanoate, lithium salt,
- (2S)-2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-5-methoxypentanoate, lithium salt,
- (2S)-2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]aminopent-4-ynoate, lithium salt,
- 375 2-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]oxy-4-methylthiobutanoate, lithium salt,
- N-[4-(N-(5-bromo-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 380 N-[4-(N-(5-phenyl-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(N-(5-(3-methoxyphenyl)-(4-chlorophenyl)furan-2-ylmethyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(N-(4,5-di(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylamino-methyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 385 N-[4-(N-(5-thien-3-yl-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(N-(2-cyclohexylethyl)-N-2-fluoroethylaminomethyl)-2-(2-methyl-

- phenyl)benzoyl]methionine, . .
- 390 N-[4-(N-(2-cyclohexylethyl)-N-2,2,2-trifluoroethylaminomethyl)-2-(2-methyl-phenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-2-methoxyethylaminomethyl)-2-(2-methyl-phenyl)benzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-2-methylthioethylaminomethyl)-2-(2-methyl-phenyl)benzoyl]methionine,
- 395 N-[4-(N-(2-cyclohexylethyl)-N-1-methyl-2(S)-methylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-2-N,N-dimethylaminomethyl)-2-(2-methyl-phenyl)benzoyl]methionine,
- 400 N-[4-(N-(1-benzyloxymethyl-2-(S)-ethylthioethylaminomethyl)-2-(2-methyl-phenyl)benzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]ornithine, trifluoroacetate salt,
N-[4-(N-(2-cyclohexylethyl)-N-2-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]thien-2-ylalanine,
- 405 N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-fluoro-2-(2-methyl-phenyl)benzoyl]methionine,
N-[4-(N-butyl-N-4-cyclohexylbenzylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
- 410 N-[4-(N-butyl-N-4-cyclohexylbenzoylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylaminocarbonyl-2-(2-methylphenyl)benzoyl)-methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
- 415 N-[4-(N-cyclohexylmethyl-N-butylaminocarbonylmethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexanoyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
- 420 N-[4-(N-cyclohexylmethyl-N-butanoylaminoethyl)-2-(2-methylphenyl)benzoyl]-methionine lithium salt,
N-[4-(N-cyclohexylpropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexyl-N-propanoylaminopropyl)-2-(2-methylphenyl)benzoyl]-methionine,
- 425 N-[4-(N-cyclohexyl-N-butylaminopropyl)-2-(2-methylphenyl)benzoyl]-

methionine, lithium salt,
N-[4-(N-cyclohexyl-N-methylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-cyclohexyl-N-butylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
430 methionine, lithium salt,
N-[4-(N,N-dicyclohexylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-adamant-1-ylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
435 N-[4-(N-adamant-2-ylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-adamant-1-ylmethylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-mytanylmethylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
440 methionine, lithium salt,
N-[4-(N-cyclooctanylaminocarbonylethyl)-2-(2-methylphenyl)-benzoyl]-methionine,
lithium salt,
3-[4-(N-cyclohexyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoylmethyl]-
4-methylthiobutyric acid,
445 N-[4-(N-butylaminocarbonylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(N-(2,2,4,4-tetramethylbutylamino)carbonylethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N,N-dibutylaminopropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium
450 salt,
N-[4-N-(2-ethylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-propylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-butylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(4-butylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
455 N-[4-N-(2-butylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-N-(2,6-diethylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-(2-butylphenyl)-N-(cyclohexylmethyl)aminomethyl-2-(2-methylphenyl)-
460 benzoyl]methionine, lithium salt,
N-[4-N-(2-cyclohexylethyl)-N-(3-methylphenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,

- N-[4-N-(2-butylphenyl)-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- 465 N-[4-N-butyl-N-(2-(3,5-difluoro)phenylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-butanefulfonyl-N-(2-phenylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt,
- N-[4-N-(2-cyclohexylethyl)-N-methylaminomethyl-2-(2-methylphenyl)benzoyl]-3-aminotetrahydrofuran-2-one,
- 470 N-[4-N-(2-cyclohexylethyl)-N-butylaminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-butyl-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine 4-methylphenylsulfonimide,
- 475 N-[4-N-butyl-N-(1-phenyltetrazol-5-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-t-butyl-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-(2-cyclohexylethyl)-N-(pent-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- 480 N-[4-N-(2-cyclohexylethyl)-N-(pent-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-(2-cyclohexylethyl)-N-propyloxyaminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 485 N-[4-N-(2-cyclohexylethyl)-N-propanesulfonylaminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-(3-chloropropanesulfonyl)-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-(2-cyclohexylethyl)-N-(3-ethoxypropanesulfonyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt,
- 490 N-[4-N-(2-cyclohexylethyl)-N-(3-trifluoromethylpropanesulfonyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-(butanesulfonyl)-N-(3-cyclohexylpropyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 495 N-[4-N-(4-cyclohexyl-1-ethylthiobutan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-N-(butanesulfonyl)-N-(4-cyclohexylbutyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-butyl-N-quinolin-2-ylaminomethyl-2-(2-methylphenyl)benzoyl]-

- 500 methionine,
N-[4-(N-butyl-N-(2-piperidin-1-ylethyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-((1-norpholinocarbonyl)butyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
505 N-[4-N-butyl-N-(2-morpholin-4-ylethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-butyl-N-(fluoren-9-yl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-N-(2-cyclohexylethyl)-N-(furan-2-ylmethyl)aminomethyl-2-(2-methyl-
510 phenyl)benzoyl]methionine,
N-[4-N-butyl-N-(2-pyrrolidin-1-ylethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-(2-butylphenyl)-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,
515 N-[4-N-((2-ethylthio)-1,3,4-thiadiazol-5-yl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-butyl-N-((2-ethylthio)-1,3,4-thiadiazol-5-yl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
520 methionine p-tolylsulfonimide, hydrochloride salt,
N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine 4-(aminomethyl)phenylsulfonimide, dihydrochloride salt,
N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, isopropylsulfonimide,
525 N-[4-N-(N-phenyl-N-(4-fluorobenzoyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(n-butanefonyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(3-nitrobenzenesulfonyl)aminomethyl)-2-(2-methyl-
530 phenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-fluorobenzenesulfonyl)aminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-ethylbenzenesulfonyl)aminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
535 N-[4-N-(N-phenyl-N-(4-nitrobenzenesulfonyl)aminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,

- N-[4-N-(N-phenyl-N-(2,3-dichlorobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 540 N-[4-N-(N-3,4-(methylenedioxy)phenyl-N-(4-fluorobenzyl)-aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-3,4-(methylenedioxy)phenyl-N-(4-fluorobenzyl)-aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(2-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 545 N-[4-N-(N-phenyl-N-(3-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(4-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(4-bromobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 550 N-[4-N-(N-phenyl-N-(4-cyanobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(4-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- 555 N-[4-N-(N-phenyl-N-(4-trifluoromethoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(4-nitrobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(4-carboxylic acid benzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, dilithium salt,
- 560 N-[4-N-(N-phenyl-N-(4-phenylbenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(4-N-carboxymethionine)benzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, dilithium salt,
- 565 N-[4-N-(N-phenyl-N-(2-naphthyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(9-methyl-anthracene-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(2-methyl-anthraquinone-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 570 N-[4-N-(N-phenyl-N-(2,3-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
- N-[4-N-(N-phenyl-N-(2,4-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)-

- benzoyl]methionine, lithium salt,
- 575 N-[4-N-(N-phenyl-N-(2-thiophenesulfonyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2-methyl-4-methylemethiazolyl)aminomethyl)-2-
(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-3,5-difluorophenyl-N-(5-thiazolylmethyl)aminomethyl)-2-
580 (2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(5-thiazolylmethyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-
(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
- 585 N-[4-N-(N-(4-acetonitrilephenyl-N-(3,5-difluorobenzyl)aminomethyl)-2-
(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(3-methoxy-5-nitrobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-nitrophenyl-N-(4-methoxybenzyl)aminomethyl)-2-(2-
590 methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-butyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4,4,4-trifluorobutyl-N-(3,5-difluorobenzyl)aminomethyl)-
2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 595 N-[4-N-(N-cyclohexyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-cyclohexanonyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-
(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-(2,2-dimethyltrimethylene ketal)-cyclohexyl)-N-(3,5-
600 difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium
salt,
N-[4-N-(N-cyclohexylmethyl-N-(2,4-difluorobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-cyclohexylmethyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-
605 methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-cyanobenzyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(3,5-difluorobenzyl)-N-(4-N-carboxymethionine)benzyl)-
aminomethyl-2-(2-methylphenyl)benzoyl]methionine, dilithium salt,
610 N-[4-N-(N-(2-cyclohexylethyl-N-(3,5-difluorobenzyl)aminomethyl)-2-

- (2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(3-methylthiopropyl)-N-(3,5-difluorobenzyl)aminomethyl)-
 2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-cyclopropyl-N-(2-(3,5-difluorophenyl)ethyl)aminomethyl)-
 2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 615 [4-N-(N-2-methylbutyl-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-
 (2-methylphenyl)benzoyl]methionine, lithium salt,
 [4-N-(N-butyl-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-(2-
 methylphenyl)benzoyl]methionine, lithium salt,
 620 N-[4-N-(N-(4-methyltetrahydropyran-yl)-N-(3,5-difluorobenzyl)-
 aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(4-methyltetrahydrothiopyran-yl)-N-(3,5-difluorobenzyl)-
 aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(4-tetrahydropyran-yl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-
 625 methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(3-cyclohexyl-1-ethylthioprop-2-yl)aminomethyl)-2-(2-
 methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
 N-[4-(N-methyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-
 methylphenyl)benzoyl]methionine, p-tolylsulfonimide,
 630 N-[4-N-(N-(trans-4-hydroxycyclohexyl)-N-(3,5-difluorobenzyl)aminomethyl)-
 2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(cis-4-hydroxycyclohexyl)-N-(3,5-difluorobenzyl)-aminomethyl)-2-
 (2-methylphenyl)benzoyl]methionine, lithium salt,
 (2S) 2-N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-
 635 methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
 N-[4-(N-(2-(1,3-dioxan-2-ylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]methionine,
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
 benzoyl]thioglutamine, lithium salt,
 640 N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-methoxy-2-(2-
 methylphenyl)benzoyl]methionine,
 N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-N,N'-dimethyl-
 amino-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-(6-fluorobenzothiazol-2-yl)aminomethyl)-2-(2-methylphenyl)-
 645 benzoyl]methionine, and
 N-[4-N-butyl-N-(furan-2-ylmethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
 methionine.

10. A compound selected from the group consisting of
- [4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine,
 - [4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine,
 - [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine,
 - methyl ester, hydrochloride,
 - [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine,
 - [4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine,
 - hydrochloride,
 - [4-(4-hydroxy-prolinyl)amino-2-phenylbenzoyl]methionine, trifluoroacetate,
 - [4-((2S,4S)-4-mercaptopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]-methionine, trifluoroacetate,
 - [4-((2S,4R)-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]-methionine, hydrochloride,
 - [4-((2S,4S)-4-thiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]-methionine, hydrochloride,
 - [4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine, trifluoroacetate,
 - [4-(piperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine, hydrochloride,
 - [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine,
 - [4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine,
 - [4-(3-piperidinecarboxyamino)-2-phenylbenzoyl]methionine, hydrochloride,
 - [4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoyl]methionine, sodium salt,
 - [4-(2-piperazinylmethylamino)-2-phenylbenzoyl]methionine,
 - [4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine lithium salt,
 - N-[4-N-2-hydroxyethylamino-2-phenylbenzoyl]methionine,
 - N-[4-(N-2-amino-3-benzoyloxypropionyl)amino-2-phenylbenzoyl]methionine,
 - N-[4-N-phenyl-N-benzylaminomethyl-2-phenylbenzoyl]methionine,
 - N-[4-N-(2-hydroxyethyl)-N-benzylaminomethyl-2-phenylbenzoyl]methionine, lithium salt,
 - N-[4-N-(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,
 - N-[4-N,N-dibenzylaminomethyl-2-phenylbenzoyl]methionine, lithium salt,
 - N-[4-N-(benzyl-N-thiazol-5-ylmethyl)aminomethyl-2-phenylbenzoyl]-methionine,

N-[4-(N-benzylaminomethyl)-2-phenylbenzoyl]methionine, hydrochloride salt,
N-[4-(4-hydroxyprolinylamino)-2-phenylbenzoyl]methionine,
N-[4-((2S,4S)-4-thiolpyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine,
N-[4-((2S,4R)-4-thiolpyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]-
methionine, lithium salt,
[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
4-(N-benzyl-N-phenyl)-aminomethyl-2-(2-methylphenyl)benzoylmethionine,
N-[4-N-(2,2-dibenzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]-
methionine, sodium salt,
N-[4-N-(2-benzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]-
methionine, sodium salt,
N-[4-N-(2-cyclohexylmethyl-3-hydroxypropyl)amino-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-(furan-2-ylmethyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-(2-benzylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-phenyl)ethyl-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-N-(3-phenyl)propyl-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-N-(2,2-diphenyl)ethyl-N-phenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-(adamantan-1-ylmethyl)-N-phenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-(2-adamantan-1-ylethyl)-N-phenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N,N-dibenzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-N-(2-phenylethyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-(3-phenoxybenzyl)-N-benzylaminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-methyl-N-(2-phenylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-benzyl-N-pyrazin-2-ylaminomethyl-2-(2-methylphenyl)benzoyl]-

methionine, lithium salt,
N-[4-N-(2-phenylethyl)-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(2-indol-3-ylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-N-(2-cyclohexyl-1-ethan-1-ol-2-yl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(1,3-diphenylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(1-cyclohexyl-6-methylhept-3-en-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(1-cyclohexyl-6-methylheptan-2-yl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(1-cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(1-cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, methyl ester,
N-[4-N-phenylacetyl-amino-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(4'-methylphenylacetyl)amino-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(4'-methoxyphenylacetyl)amino-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-N-(3-phenylpropionoyl)amino-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(3-(2-methoxyphenyl)propionoyl)amino-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-N-benzyl-N-(thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine,
N-[4-N-benzyl-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine,

N-[4-(2-cyclohexylethan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(N-benzyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, trifluoroacetate salt,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-acetyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-(N,N-dimethylaminocarbonyl)-N-(2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-methanesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-benzenesulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt,
N-[4-(3-cyclohexylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(4-cyclohexylbutan-3-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(6-cyclohexylhexan-5-ylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(1,2-dicyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, trifluoroacetate salt,
N-[4-(2-cyclohexylprop-1-en-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methanesulfonylbutanoic acid, lithium salt,
N-[4-(3-cyclohexyl-1-t-butylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(3-cyclohexyl-1-phenylthioprop-2-ylaminomethyl)-2-(2-methylphenyl)-

benzoyl]methionine, lithium salt,
N-[4-N-benzoyl-N-2-cyclohexylethylaminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-t-butyloxycarbonyl-N-2-cyclohexylethylaminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
pivaloyloxymethyl N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-methyl-
aminomethyl-2-(2-methylphenyl)benzoyl]methionine, hydrochloride salt,
N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-methylaminomethyl-2-
(2-methylphenyl)benzoyl]-N-methylmethionine, lithium salt,
N-[4-N-(3-cyclohexyl-1-cyclohexylthiopropyl)-N-methylamino-
methyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(3-cyclohexyl-1-(2-methylphenyl)thiopropyl)-N-methyl-
aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-toluenesulfonylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(3-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzenesulfonyl)aminomethyl)-
2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-chlorobenzyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzyl)aminomethyl)-2-(2-
methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,
N-[4-(1-ethoxycarbonylpiperidin-4-ylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-[3-methylthio-1-carboxyprop-2-yl]aminocarbonyl)-2-phenylbenzoyl]-
methionine,
N-[4-N-(furan-2-ylmethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(furan-3-ylmethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-3-methoxyphenylaminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(2-phenylethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)-

benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-(1,3-benzodiox-5-yl)-N-pyrimidin-5-ylaminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-(1,3-benzodiox-5-yl)-N-pyridizin-2-ylaminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(2-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(4-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(4-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-benzyl-N-(3-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-benzyl-N-(4-nitrophenyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]-
methionine, lithium salt,
N-[4-N-(N-benzyl-N-(2-acetylphenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-benzyl-N-(3-acetylphenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-benzyl-N-(2-chlorophenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-benzyl-N-(3-chlorophenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(N-benzyl-N-(4-chlorophenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(2-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-benzyl-N-(2-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(3-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(4-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-benzyl-N-(4-trifluoromethylphenyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,

N-[4-N-(4-piperidin-1-ylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-N-(4-morpholin-1-ylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-N-(4-phenoxyphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-N-(benzyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(toluenesulfonyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(methanesulfonyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-2-cyclohexylethyl-N-cyclopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-tetrahydrothiopyran-4-yl-N-thiazol-5-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-t-butyloxycarbonyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(3-cyclohexyl-1-oxo-1-piperidin-1-ylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(1-ethylthio-4-methylpentan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(1-ethylthio-4-methylpentan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(1,3-dicyclohexylpropan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(1,3-dicyclohexylpropan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-acetyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-benzoyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-benzenesulfonyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(N,N-dibutylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(N-(N,N-dibutylacetamido)-N-methylaminomethyl)-2-(2-methylphenyl)-

benzoyl]methionine,
N-[4-(N-(N,N-dibenzylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(N-(2-cyclohexylethyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(N-butanefonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-(N,N-dibutylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-butanefonyl-N-(3-phenylpropyl)aminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-methylaminomethyl-2-
(2-methylphenyl)benzoyl]methionine, hydrochloride,
N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-isobutylaminomethyl-
2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(3-cyclohexyl-1-ethylthiopropyl)-N-formylaminomethyl-2-
(2-methylphenyl)benzoyl]methionine,
N-[4-N-acetyl-N-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-N-t-butylloxycarbonyl-N-(3-cyclohexyl-1-ethylthiopropyl)amino-
methyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-benzoyl-N-(3-cyclohexyl-1-ethylthiopropyl)aminomethyl-2-(2-
methylphenyl)-benzoyl]methionine,
N-[4-N-butanefonyl-N-(3-cyclohexyl-1-ethylthiopropyl)amino-
methyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-benzenesulfonyl-N-(3-cyclohexyl-1-ethylthiopropyl)amino-
methyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-5-(4-chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-
2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-methyl-N-(1,1-dimethyl-2-phenylethyl)aminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-(N-methyl-N-(1,1-dimethyl-2-cyclohexylethyl)aminomethyl)-2-(2-
methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-2-cyclohexylethyl-N-thiazol-5-ylmethylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-(1-ethylthio-4-phenylbut-2-oxymethyl)-2-(2-methylphenyl)-benzoyl]-

methionine,
N-[4-N-benzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-N-benzyl-N-(4-carboxamidophenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-sulfonamidophenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-N-benzoylsulfonamidophenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-propionylphenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-benzoylphenyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-benzyl-N-(4-(6-methylbenzthiazol-2yl)phenyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-2,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-2,4-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-vinylphenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-acetylphenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxyethyl)phenyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxy-1-phenylmethyl)phenyl)-
aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(4-(2-tert-butyl dimethylsiloxyethyl)phenyl)-
aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-3,5-difluorobenzyl-N-(1-ethylthio-3-cyclohexylprop-2-yl)amino-
methyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-N-piperidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,

N-[4-(2-N-2-methoxymethylpyrrolidin-1-ylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(4-trans-pentafluorophenoxy)cyclohexyl]aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]glutamine, trifluoroacetic acid salt,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]homocysteine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]histidine, trifluoroacetic acid salt,
N-[4-(N-cyclohexylmethylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N,N-di-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-phenylacetylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-1-adamantanoylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-t-butoxycarbonylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-2-ethylhexyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-2,2,2-trichloroethoxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-cyclohexyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-adamantyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-phenoxy carbonylaminoethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-benzyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-adamant-1-aminocarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-adamant-1-aminothiocarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-

benzoyl]glutaminitrile, lithium salt,
N-[4-(N-p-toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-(4-benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)-
aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
(2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
(2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-
methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-
benzoyl]norleucine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N,N-dimethylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
(2S) 2-N-[4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)-
benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-p-toluenesulfonylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-m-toluenesulfonylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-p-tert-butylbenzenesulfonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-p-bromobenzenesulfonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-p-methoxybenzenesulfonylaminomethyl)-2-
(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-p-nitrobenzenesulfonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexyl-2-methylpropyl)-N-methylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-(3-cyclohexyl-1-methoxyprop-2-ylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(1-ethylsulfonyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
(2S)-2-N-[4-(1-ethylsulfonyl-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methyl-
phenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,

N-[4-(N-(3-cyclohexylpropyl)-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-glucosaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
(2S)-2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-difluoromethylthiobutanoate, lithium salt,
(2S)-2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-5-methoxypentanoate, lithium salt,
(2S)-2-N-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]aminopent-4-ynoate, lithium salt,
2-[4-(N-2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]oxy-4-methylthiobutanoate, lithium salt,
N-[4-(N-(5-bromo-(4-chlorophenyl)furan-2-yl)methyl-N-isopropyl-aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(5-phenyl-(4-chlorophenyl)furan-2-yl)methyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(5-(3-methoxyphenyl)-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(4,5-di(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylamino-methyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(5-thien-3-yl-(4-chlorophenyl)furan-2-yl)methyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-2-fluoroethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-2,2,2-trifluoroethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-(2-cyclohexylethyl)-N-2-methoxyethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-2-methylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-1-methyl-2(S)-methylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-2-N,N-dimethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(1-benzyloxymethyl-2-(S)-ethylthioethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)-

benzoyl]ornithine, trifluoroacetate salt,
N-[4-(N-(2-cyclohexylethyl)-N-2-N-methylaminomethyl)-2-(2-methylphenyl)-
benzoyl]thien-2-ylalanine,
N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-fluoro-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-(N-butyl-N-4-cyclohexylbenzylaminomethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-butyl-N-4-cyclohexylbenzoylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-butylaminocarbonylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexanoyl-N-butylaminoethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-cyclohexylmethyl-N-butanoylaminoethyl)-2-(2-methylphenyl)benzoyl]-
methionine lithium salt,
N-[4-(N-cyclohexylpropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexyl-N-propanoylaminoethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(N-cyclohexyl-N-butylaminopropyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-cyclohexyl-N-methylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-cyclohexyl-N-butylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N,N-dicyclohexylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-adamant-1-ylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-adamant-2-ylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-adamant-1-ylmethylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-mytanylmethylaminocarbonylethyl)-2-(2-methylphenyl)benzoyl]-

methionine, lithium salt,
N-[4-(N-cyclooctanylaminocarbonyl)ethyl]-2-(2-methylphenyl)-benzoyl]-methionine,
lithium salt,
3-[4-(N-cyclohexyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoylmethyl]-
4-methylthiobutyric acid,
N-[4-(N-butylaminocarbonylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(N-(2,2,4,4-tetramethylbutylamino)carbonyl)ethyl]-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(N,N-dibutylaminopropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium
salt,
N-[4-N-(2-ethylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-propylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-butylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(4-butylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-butylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-N-(2,6-diethylphenyl)-N-(3,5-difluorobenzyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine, lithium salt,
N-[4-N-(2-butylphenyl)-N-(cyclohexylmethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-(2-cyclohexylethyl)-N-(3-methylphenyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-N-(2-butylphenyl)-N-(2-cyclohexylethyl)aminomethyl-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-N-butyl-N-(2-(3,5-difluoro)phenylethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-N-butanefonyl-N-(2-phenylethyl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine lithium salt,
N-[4-N-(2-cyclohexylethyl)-N-methylaminomethyl-2-(2-methylphenyl)-
benzoyl]-3-aminotetrahydrofuran-2-one,
N-[4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-N-butyl-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]-
methionine 4-methylphenylsulfonimide,
N-[4-N-butyl-N-(1-phenyltetrazol-5-yl)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine,

N-[4-N-t-butyl-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine,
N-[4-N-(2-cyclohexylethyl)-N-(pent-2-yl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine,
N-[4-N-(2-cyclohexylethyl)-N-(pent-2-yl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine,
N-[4-N-(2-cyclohexylethyl)-N-propyloxyaminomethyl-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(2-cyclohexylethyl)-N-propanesulfonylaminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(3-chloropropanesulfonyl)-N-(2-cyclohexylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-cyclohexylethyl)-N-(3-ethoxypropanesulfonyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt,
N-[4-N-(2-cyclohexylethyl)-N-(3-trifluoromethylpropanesulfonyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(butanesulfonyl)-N-(3-cyclohexylpropyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(4-cyclohexyl-1-ethylthiobutan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(butanesulfonyl)-N-(4-cyclohexylbutyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-butyl-N-quinolin-2-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-butyl-N-(2-piperidin-1-ylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-((1-norpholinocarbonyl)butyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-butyl-N-(2-morpholin-4-ylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-butyl-N-(fluoren-9-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-cyclohexylethyl)-N-(furan-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-butyl-N-(2-pyrrolidin-1-ylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N-(2-butylphenyl)-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methyl-

phenyl)benzoyl]methionine,
N-[4-N-((2-ethylthio)-1,3,4-thiadiazol-5-yl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine,
N-[4-N-butyl-N-((2-ethylthio)-1,3,4-thiadiazol-5-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]-methionine p-tolylsulfonimide, hydrochloride salt,
N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine 4-(aminomethyl)phenylsulfonimide, dihydrochloride salt,
N-[4-(N-butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, isopropylsulfonimide,
N-[4-N-(N-phenyl-N-(4-fluorobenzoyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(n-butanesulfonyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(3-nitrobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt, .
N-[4-N-(N-phenyl-N-(4-fluorobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-ethylbenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-nitrobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2,3-dichlorobenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-3,4-(methylenedioxy)phenyl-N-(4-fluorobenzyl)-aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-3,4-(methylenedioxy)phenyl-N-(4-fluorobenzyl)-aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(3-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-fluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-bromobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,

N-[4-N-(N-phenyl-N-(4-cyanobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-trifluoromethoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-nitrobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-carboxylic acid benzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, dilithium salt,
N-[4-N-(N-phenyl-N-(4-phenylbenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(4-N-carboxymethionine)benzyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, dilithium salt,
N-[4-N-(N-phenyl-N-(2-naphthyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(9-methyl-anthracene-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2-methyl-anthraquinone-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2,3-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2,4-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2-thiophenesulfonyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(2-methyl-4-methylemethiazolyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-3,5-difluorophenyl-N-(5-thiazolylmethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(5-thiazolylmethyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-acetonitrilephenyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-phenyl-N-(3-methoxy-5-nitrobenzyl)aminomethyl)-2-(2-

methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-nitrophenyl)-N-(4-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-butyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4,4,4-trifluorobutyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-cyclohexyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-cyclohexanonyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-(2,2-dimethyltrimethylene ketal)-cyclohexyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-cyclohexylmethyl-N-(2,4-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-cyclohexylmethyl-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-cyanobenzyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(3,5-difluorobenzyl)-N-(4-N-carboxymethionine)benzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, dilithium salt,
N-[4-N-(N-(2-cyclohexylethyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(3-methylthiopropyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-cyclopropyl-N-(2-(3,5-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
[4-N-(N-2-methylbutyl-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
[4-N-(N-butyl-N-(2-(2,4-difluorophenyl)ethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-methyltetrahydropyran-yl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-methyltetrahydrothiopyran-yl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-(N-(4-tetrahydropyran-yl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-

methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(N-(3-cyclohexyl-1-ethylthioprop-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
 N-[4-(N-methyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, p-tolylsulfonimide,
 N-[4-N-(N-(trans-4-hydroxycyclohexyl)-N-(3,5-difluorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-(N-(cis-4-hydroxycyclohexyl)-N-(3,5-difluorobenzyl)-aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 (2S) 2-N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methylsulfonylbutanoate, lithium salt,
 N-[4-(N-(2-(1,3-dioxan-2-ylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]thioglutamine, lithium salt,
 N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-methoxy-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-5-N,N'-dimethylamino-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-N-(6-fluorobenzothiazol-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, and
 N-[4-N-butyl-N-(furan-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine.

11. A compound according to claim 10 selected from the group consisting of [4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt, and N-[4-(N-(2-cyclohexylethyl)-N-butylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt.
12. A method of inhibiting protein isoprenyl transferases in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
13. A composition for inhibiting protein isoprenyl transferases comprising a

pharmaceutical carrier and a therapeutically effective amount of a compound of claim 1.

14. A method for inhibiting or treating cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1 alone or in combination with another chemotherapeutic agent.
15. A composition for the treatment of cancer comprising a compound of claim 1 in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.
16. A method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
- 5 17. A composition for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both comprising a compound of claim 1 in combination with a pharmaceutical carrier.
- 5 18. A method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
19. A composition for treating or preventing restenosis in a mammal comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/09296

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database HCAPLUS on STN, 1997:247953, BOYLE, F.T. et al. 'Preparation of 2-aminomethyl-4-mercaptopyrrolidines and analogs as farnesyl transferase inhibitors', 20 February 1997, PCT Int. Appl. 189 pp., see the entire abstract.	1-19
X	Database HCAPLUS on STN. 1996:567259 SEBTI et al. 'Peptidomimetic inhibitors of prenyl transferase, preparation and activity of the peptidomimetics, and use for treating tumors', 18 July 1996, PCT Int. Appl 186 pp., see the entire abstract.	1-19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 SEPTEMBER 1998

Date of mailing of the international search report

16 OCT 1998

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/09296

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/38, 31/39, 31/40, 31/415, 31/42, 31/425, 31/44, 31/445, 31/495, 31/505, 31/095, 31/18; C07D 207/09, 233/54, 239/24, 241/04, 263/02, 277/28, 307/00, 333/00, 209/10;
C07C 303/00, 307/00, 309/00, 311/00, 313/00

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/255, 256, 331, 351, 357, 371, 400, 419, 423, 424, 439, 447, 461, 570, 604; 544/335, 400 ; 546/225, 300, 312, 336;
548/196, 338.1, 495, 543; 549/69, 76, 491; 564/42, 49

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/255, 256, 331, 351, 357, 371, 400, 419, 423, 424, 439, 447, 461, 570, 604; 544/335, 400 ; 546/225, 300, 312, 336;
548/196, 338.1, 495, 543; 549/69, 76, 491; 564/42, 49